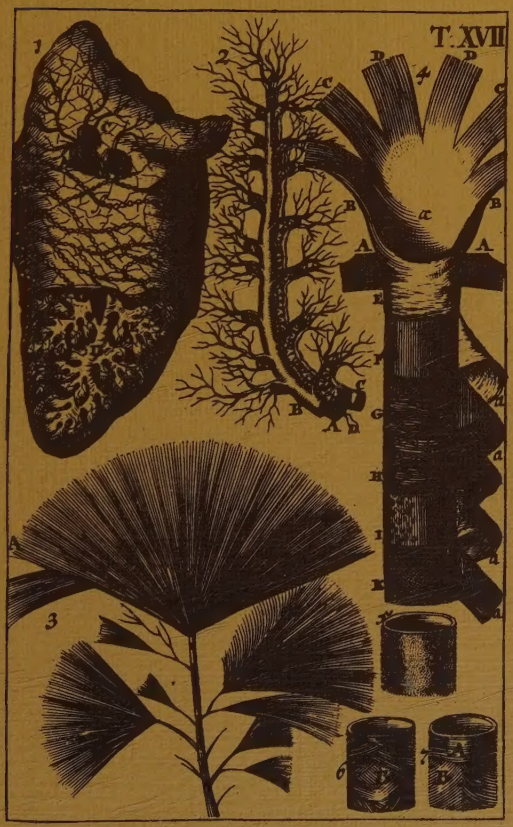
FUNCTIONAL AND THERAPEUTIC STUDIES IN PROGRESSIVE SYSTEMIC SCLEROSIS

Berith Blom-Bülow



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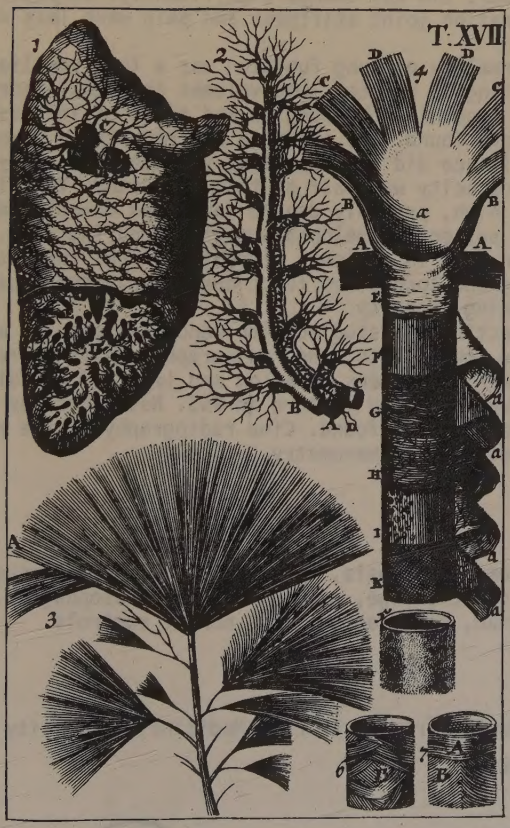

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FUNCTIONAL AND THERAPEUTIC STUDIES IN PROGRESSIVE SYSTEMIC SCLEROSIS

Progressive systemic sclerosis (PSS) involves skin, joints, muscles and visceral organs. Many drugs have been tried in PSS, but no treatment has been proven effective in controlled studies. Open trials suggested that cyclofenil, a weak non-steroidal oestrogen, was effective in PSS. A double-blind crossover study in 2x6 months was made in 38 patients with generalized disease. The data collected before treatment were used in a comprehensive study of the lung function, working capacity and esophageal function. Twenty-seven patients completed both periods.

The general condition after the drug was significantly improved as compared to that after placebo. Esophageal peristalsis improved. Other important parameters did not change significantly. In patients with a short disease duration joint stiffness and pain were less during drug treatment.

The main abnormality of lung function was a less compliant lung parenchyma resulting in reduced lung volumes and ventilatory capacity. A mild intrinsic bronchial obstruction and signs of increased bronchial wall stiffness were found. Gas exchange was remarkably normal at rest. Static lung compliance did not correlate to chest radiology.

Mean working capacity was half of that predicted. Ventilation at maximal work was high, probably due to increased muscular metabolism. One third of the patients developed arrhythmia during work. Myocardial damage was common also in patients without clinical infarction. Circulation, lung and locomotive functions contributed equally to the reduction of working capacity.

Esophageal function was studied with manometry also in matched controls, and was compared to cine radiography. Resting pressures in the upper and lower sphincters were low and impaired coordination of the peristalsis was an early feature in PSS. Neuromuscular dysfunction of the whole esophagus was found. Cine radiography of the recumbent patient correlated well to manometry.

Key-words

Progressive systemic sclerosis, cyclofenil, controlled study, pulmonary function, blood gas exchange, working capacity, esophageal function, chest roentgenogram, cine radiography, normal controls.

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To my parents

The present thesis is based on the following papers which will be referred to in the text by their Roman numerals.

I Blom-Bülow, B., Öberg, K., Wollheim, F.A., Persson, B., Jonson, B., Malmberg, P., Boström, H. and Herbai, G.
Cyclofenil versus placebo in progressive systemic sclerosis. A one year double-blind crossover study of 27 patients.
Acta Med Scand 210, 419-428, 1981.

II Blom-Bülow, B., Jonson, B. and Brauer, K.
Lung function in progressive systemic sclerosis.
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III Blom-Bülow, B., Jonson, B. and Brauer, K.
Factors limiting physical performance in progressive systemic sclerosis.
Accepted for publication in Semin Arthritis Rheum, 1983.

IV Blom-Bülow, B., Sundström, G., Jonson, B., Tylén, U. and Wollheim, F.A.
Early changes in esophageal function in progressive systemic sclerosis.
Submitted for publication.

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ABBREVIATIONS

ALAT	alanine aminotransferase
ANA	anti-nuclear antibodies
ASAT	aspartate aminotransferase
BF_{max}	breathing frequency at maximal work
$Cdyn_L$	dynamic pulmonary compliance
Cst_L	static lung compliance
$\Delta AaPO_2$	alveolo-arterial oxygen pressure difference
ΔBE	fall in base excess during work
ΔWC	deficit in working capacity in % of that predicted
FEV_1	forced expiratory volume in 1 sec
FRC	functional residual capacity
GT	gamma glutamyl transferase
HLA	human leukocyte antigen - group A
HR_{max}	heart rate at maximal work
LES	lower esophageal sphincter
NS	not significant
Pel_L	static elastic recoil pressure
PSS	progressive systemic sclerosis
P/V curve	static elastic pressure-volume curve
$\dot{Q}s/\dot{Q}t$	intrapulmonary shunt
r	correlation coefficient
Rf_L	functional pulmonary resistance
R_L	pulmonary resistance
RNP	ribo-nucleo-proteine
RV	residual volume
TLC	total lung capacity
UES	upper esophageal sphincter
VC	vital capacity
$\dot{V}_E$	ventilation
V_D	physiological dead space
V_T	tidal volume
%p	per cent of predicted normal value

INTRODUCTION

Progressive systemic sclerosis (PSS, scleroderma) is an uncommon, but not rare, disease that to varying degrees involves the skin and organs of the viscera. The clinical picture of PSS can be very complex, and give rise to both diagnostic and therapeutic problems.

The clinical course shows much variation and has several different stages. Raynaud's phenomenon often precedes the actual clinical manifestation, starting with an oedematous stage, followed by an indurative and an atrophic stage. It is a progressive disease which, depending on the type of engagement of different organs, leads to invalidity for a shorter or longer period of time.

The etiology of PSS is not clear, and it is classified with other disorders of unknown etiology such as rheumatoid arthritis, systemic lupus erythematosus and dermatomyositis in the group of connective tissue diseases.

Cases of PSS have been described in ancient medical works. Hippocrates (460-370 B.C.) wrote about "a certain Athenian whose skin was so indurated that it could not be pinched", and Galen (130-200 A.D.) described an illness characterized by "a sort of obstruction of the pores of the skin with thickening, white spots, pigmentations and absence of sweat glands". These descriptions might well refer to cases of PSS. It was Carlo Curzio who, in 1753,published the first convincing description of the disease. G. Fantonetti gave the disease its name by publishing an article entitled "Skleroderma Generale" in 1836 (Barnett 1974; Rodnan & Benedek 1978).

At that time, scleroderma was generally regarded as a disorder of the skin and of the peripheral circulation. In the late Nineteenth Century, there were several reports of lung fibrosis in PSS. The awareness that scleroderma was one manifestation of a generalized disease lead Goetz to propose the name progressive systemic sclerosis in 1945 (Goetz 1945).

In recent years, increasing interest has been given to the function of the different organ systems involved, as well as to the etiology of PSS.

In 1980 the American Rheumatism Association's Diagnostic and Therapeutic Committee published preliminary criteria for the classification of systemic sclerosis, which are based on an American multicenter study of early diagnosed cases of systemic sclerosis that is now being conducted.

The proposed criteria are either the sole major criterion, proximal scleroderma, or two or more of the three minor criteria: a) sclerodactyly, b) digital pitting scars on the finger tips or loss of substance of the distal finger pad, and c) bilateral basal pulmonary fibrosis (Table 1). These criteria have a 97 % sensitivity and a 98 % specificity for definite systemic sclerosis. When distal esophageal hypoperistalsis was used as an additional minor criterion, it did not improve the overall discrimination in this study (Masi et al. 1980).

Table 1. Clinical signs used in the classification of systemic sclerosis according to the American Rheumatism Association (1980).

1. Major criterion:

   Proximal scleroderma, i.e. skin tightness, thickening and non-pitting induration at proximal portions of the extremities, the face, neck or trunk.

2. Minor criteria:

   a) Sclerodactyly: The above indicated changes limited to the fingers and toes.
   b) Digital pitting scars or loss of substance from the finger pad.
   c) Bilateral basal pulmonary fibrosis on chest roentgenogram not attributable to primary lung disease.

EPIDEMIOLOGY

PSS is prevalent in all areas of the world and no racial differences have been observed. Different studies in the USA have reported a mean annual incidence ranging from 2.7 to 12 cases per million inhabitans (Kurland et al. 1969; Medsger & Masi 1971).

There are no earlier reports on the incidence in Sweden. We found eight patients (sex female, two male) with PSS at autopsy during 1970-1979 in Malmö, a community of 250 000 inhabitans. The autopsy rate was more than 90 % during that period. If the population of Malmö can be regarded as static, these figures lead to an estimated annual incidence of approximately 4 cases per one million inhabitants. The prevalence of PSS in Sweden seems to correspond to the data from the USA. The female incidence exceeds the male by 3:1, as in other reports.

PSS is more common among miners and others who are occupationally exposed to coal and/or silica dust (Erasmus 1957; Rodnan 1963). A scleroderma-like condition is seen in workers exposed to polyvinyl-chloride (Black et al. 1983).

Medsger et al. (1971) studied an extensive PSS material with respect to the clinical course and the prognosis. The course of the disease varies and is marked by remissions and exacerbations. PSS progresses more rapidly in men than in women. Renal, cardiac and pulmonary involvement are each independently correlated to decreased time of survival. Renal failure in PSS is the most serious prognostic sign. When kidney involvement is diagnosed, the patients almost always die within a few months. The second most important factor for life-span prognosis is heart involvement. If the heart is involved, there is little difference in the expected life-span if there is lung involvement or not. Pulmonary engagement can be rated as the third most important prognostic factor.

The following evidences of disease are particularly prominent in some patients:

Calcinosis,
Raynaud's phenomenon,
Esophageal dysfunction,
Sclerodactyly and
Teleangiectasis.

This clinical picture is called the *CREST* syndrome. Some authors claim that CREST patients have a relatively better prognosis than other PSS patients, as visceral involvement tends to occur later on (Winterbauer 1964; Steen, Medsger & Rodnan 1982). This has, however, been disputed by others. The CREST patients are liable to develop severe pulmonary hypertension (Salerni et al. 1977) and biliary cirrhosis (Reynolds et al. 1971). There is also an increased rate of Sjögren's syndrome among these patients (Cipoletti et al., 1977).

PATHOPHYSIOLOGY - CURRENT THEORIES

The role of autoimmunity

Antibodies to nuclear RNP, often resulting in a "speckled" type of fluorescences are seen in 60-80 % of the patients with PSS. In individual patients, ANA often vary from time to time between zero and very high titres, but show no correlation to the severeness or duration of the disease (Jordon et al. 1971). Certain immunologic components that are more specific for PSS have been defined. It has been shown that sera from PSS patients react to particular nuclear antigens. The PSS sera contain anti-centromere and anti-scleroderma-70 antibodies. These specific anti-nuclear antibodies will probably be helpful in the diagnosis. They have not been shown to play a role in the pathogenesis of PSS (Tan et al. 1980; Moroi et al. 1980; McCarty et al. 1983; Douvas, Achten & Tan 1979).

Genetic susceptibility to PSS

It has been shown that PSS is linked to HLA markers. PSS patients have a combination of the two antigens B8 and DR3 more often than the general population, and an increased frequency of DR5 (Kallenberg, van der Voort-Beelen & D'Amaro 1981; Gladman et al. 1981). It has recently been reported that vinyl-chloride workers with a scleroderma-like syndrome have an increased frequency of HLA DR5. No anti-centromere or anti-scleroderma-70 antibodies were found in any of the vinyl-chloride-exposed patients (Black et al. 1983).

A familial occurrence of PSS has only been reported a few times. PSS must in actual practice be regarded as a non-inheritable disease (Leonhardt 1961; Burge, Perry & Stickler 1969).

Collagen metabolism

The scleroderma skin fibroblast in vitro produces more soluble collagen than normal cells. The total collagen-production is increased four times compared to normal (LeRoy, McGuire & Chen 1974). The 24-hour urine excretion of hydroxyproline can be used as an approximate indicator of disease activity. All patients with high excretion have a diffuse and progressive skin involvement (Stachon 1975).

Kondo, Rabin and Rodnan (1976) showed that T-lymphocytes make up the majority of lymphocytes in the skin of PSS patients. The T-cells are activated by unknown stimuli and produce lymphokines which specifically attract and stimulate collagen deposition by fibroblasts. The authors conclude that the observation that lymphocyte mediators can stimulate collagen synthesis is intriguing and suggest that a cell-mediated immune response to skin antigens may be a factor in the pathogenesis of diffuse scleroderma (Kondo et al. 1976).

The vascular theory

Raynaud's phenomenon is seen in more than 90 % of the PSS patients. Maricq et al. (1980) observed abnormal capillaries in vivo in PSS patients. Malignant hypertension is not uncommon (Lopéz-Ovejero et al. 1979). The sites of vascular involvement are small arteries, veins and capillaries. It is obvious that vascular changes occur early in the development of PSS, and that they may be related to many other manifestations of the disease. It is not known to what extent vascular involvement is a main patho-genetical factor, as was suggested by Norton and Nardo (1970).

TREATMENT OF PSS

As we have no understanding at all of the pathogenesis of PSS, its treatment has lagged behind that of other rheumatic diseases. During the last decades, a large number of drugs have been tried in PSS (Table 2). Only a few controlled studies have been performed.

Harris and Sjoerdsma made the first D-penicillamine therapy trial in PSS patients as early as 1966. Although several authors have reported improvement in 70 % to 100 % of the patients, no controlled study has as yet been performed (Harris & Sjoerdsma 1966; Bluestone et al. 1970; Mellstedt et al. 1977; Rodnan 1981; Steen, Medsger & Rodnan 1982).

Among the controlled studies, para-amino-benzoate treatment for six months led to a significant increase of skin mobility. All other clinical and laboratory parameters were unchanged (Bushnell et al. 1966). Reserpine (McFadyen, Housley & MacPherson 1973), dextrotyroxine (Winkelmann et al. 1965) and N-acetylcysteine (Furst et al. 1979) did not have any effect on the disease. Cholchicine has been claimed to show "evidence of improvement versus placebo" (Alarcón-Segovia et al. 1974), but an open study conducted later on has failed to confirm this assertion (Guttadauria, Diamond & Kaplan 1977).

Our own controlled study of cyclofenil versus placebo showed an improvement of general condition after the active drug period. Esophageal peristalsis improved significantly. In patients with a disease duration of five years or less, joint stiffness and pain improved with drug treatment (I).

Efforts have been made to treat Raynaud's phenomenon with nonpharmacological means, e.g. sympathectomy, plasmapheresis or hyperbaric oxygen therapy (Evans, Rubitsky & Perry 1953; Dau, Kahaleh & Sagebiel 1981; Copeman & Ashfield 1967). Surgical sympathectomy can not be recommended, as digital blood flow and warmth revert to preoperative values shortly after the denervation (D'Angelo 1974).

As renal engagement is always rapidly fatal, and is not always associated with severe manifestations in other organs, renal transplantations have been performed. The results motivate an aggressive approach in selected

Table 2. Review of some of many drugs tried in the treatment of PSS.
** Indicates a controlled double-blind study.*

Anti-inflammatory agents	
Corticosteroids	Evans et al. 1953, Asboe-Hansen 1982
Salicylates	D'Angelo 1974
Indomethacin	D'Angelo 1974
Potassium para-aminobenzoate	Zarafonetis 1964 *Bushnell et al. 1966
Vasoactive agents	
Reserpine	Fuleihan et al. 1968, Willerson et al. 1970, *McFadyen et al. 1973
Hydralazine	Asboe-Hansen 1982
Hormones	
Gestagens	Holzmann et al. 1968, Rau et al. 1972
Relaxin	Casten & Boucek 1958
D-thyroxine	*Winkelmann et al. 1965 Asboe-Hansen 1982
Cyclofenil	Herbai et al. 1977, Blom-Bülow et al. 1980, *Blom-Bülow et al. 1981 (I)
Immunosuppressive agents	
Azathioprine	Jansen et al. 1968
Chlorambucil	Mackenzie 1970, Steigerwald 1974
Cyclophosphamide (+ plasmapheresis)	Dau et al. 1981
Lathyrogen	
D-penicillamine	Harris & Sjoerdsma 1966, Bluestone et al. 1970, Mellstedt et al. 1977, Rodnan 1981, Asboe-Hansen 1982, Steen et al. 1982
Miscellaneous	
Colchicine	*Alarcón-Segovia et al. 1974, Guttadauria et al. 1977, Alarcón-Segovia et al. 1979
Dextran 40	Holti 1965, Kirk & Dixon 1969
Salazopyrin	Dover 1971
N-acetylcysteine	*Furst et al. 1979
Prostaglandin E_1	Martin & Tooke 1982

cases (Keane, Danielson & Raij 1976; LeRoy & Fleischmann 1978; Lam et al. 1978).

There are several problems connected with the evaluation of therapeutic effectiveness in PSS: It is an uncommon disease; most studies have been done with only a few patients and the patient material is heterogenous. The disease often progresses slowly, but spontaneous remissions make it difficult to predict the clinical course. We still lack adequate methods for the quantitative assessment of skin involvement, and the symptoms of the disease show a marked seasonal variation.

AIMS OF THE PRESENT STUDY

Observations made in open clinical studies suggested that cyclofenil had therapeutic effects in PSS (see Discussion, page 21), which motivated a controlled study. In such a study, it was considered essential to collect objective data describing detailed function of several organ systems. Data collected before cyclofenil or placebo treatment were apt to give a more comprehensive picture of the lung function, working capacity and esophageal function than those obtained in previous studies. The aims of the present study established from this background were:

To evaluate therapeutic and side-effects of cyclofenil versus placebo in a 2 x 6 months double-blind cross-over study in PSS (I).

To describe lung mechanics and gas exchange at rest and during exercise (II).

To evaluate the extent to which the manifestations from heart and lungs, joints and muscles contribute to limitation of physical activity in PSS (III).

To study the characteristics of esophageal dysfunction more closely than in previous manometric studies, and to evaluate the use of esophageal manometry and cine radiography as diagnostic tools (IV).

PATIENTS AND METHODS

SELECTION OF PATIENTS

In order to obtain a material of patients suitable for the study of cyclofenil, a co-operative study between Lund-Malmö and Uppsala was organized (I). Twenty-four patients in Lund-Malmö and fourteen in Uppsala entered the trial, which started in April, 1977. The patients fulfilled the following criteria: typical sclerodermatous skin changes, a history of Raynaud's phenomenon or sensitivity to cold, and engagement of at least one

visceral organ. Voluntary consent was obtained from all patients and the study was approved by the Ethical Committee of the University of Lund.

The 24 patients from Lund participated in studies of lung function, physical capacity and esophageal function (II-IV). Two patients were excluded from study III as they could not perform the exercise test (Nos. 2 and 34). Three patients were excluded from the esophagus study (IV) due to technical problems during the esophageal manometry (Nos. 1, 2 and 19). The patients' identification numbers are the same in studies II-IV.

To provide a reference material, a group of healthy subjects was examined with esophageal manometry. The subjects were matched to the PSS patients in regard to sex, age and smoking habits.

METHODS

A thorough clinical and laboratory evaluation was performed at the beginning of study I, and after the first and second 6 months-periods. Subjective criteria were used for assessing general well-being: feeling of chilliness, fatigue, headache, menstrual irregularities and sexual function.

The recorded skin involvement included ulcerations, oedema of fingers or hands, hair loss, abnormal pigmentation and teleangiectasis. Skin elasticity was measured with a suction-cup apparatus, according to Bluestone et al. (1970).

Hand function was assessed by a standardized measurement of dorsal extension, volar flexion, supination, pronation and hand opening. Grip strength was measured at maximal compression of a blood pressure cuff inflated to 30 mm Hg, according to Lee et al. (1974) (I).

Pulmonary function tests (I, II) included VC and FEV_1, measured with a Bernstein spirometer. TLC, RV and FRC were measured with a body plethysmograph. An esophageal balloon was used for measurements of pulmonary resistance and static elastic recoil pressure. Elastic properties of the lungs were assessed from esophageal pressure at different lung volumes. The pulmonary static elastic pressure volume curve was determined in the

body plethysmograph, and the static compliance of the lungs was measured over the interval of the pressure volume curve from 5 to 15 cm H_2O.

Pulmonary mechanics were studied during a graded exercise test. The flow at the airway opening was measured with a Fleisch pneumotachograph, and the transpulmonary pressure with an esophageal balloon.

Particular efforts were made to exclude the possibility that esophageal disease would reduce the validity of esophageal pressure as an estimate of pleural pressure (II).

Arterial blood gases were analyzed immediately after sampling. Oxygen saturation of hemoglobine was then calculated from arterial pO_2, pH and base excess. Physiological dead space at rest was calculated from the composition of mixed expired gas and from average $PaCO_2$, determined in samples drawn during the gas-collection period (II).

The exercise test was done on a bicycle ergometer. After 4 min, an arterial blood sample was taken. Pulmonary mechanics was then measured. The load was increased step-wise until symptom limitation, or until heart arrhythmia indicated that the exercise ought to be stopped. The ECG was continuously registered during work, and up to 20 min after cessation. Subjective assessments of muscle fatigue, weakness, pain, general exhaustion and dyspnoea were recorded, as well as subjective and objective reasons for stopping work (III).

Esophageal function was examined by radiography, including barium swallow examination recorded on full-size films and cine fluorography. Esophageal motility, including the activity in the upper and the lower esophageal sphincter, was studied with a central-hole catheter device (IV).

PREDICTED NORMAL VALUES

Most of our results are reported in per cent of the predicted values, in order to account for variations of sex, age, height, weight, etc. Individual values outside the 95 % interval of confidence, corresponding to 1.96 SD, are classified as abnormal.

STATISTICAL METHODS

Student's t-test, for paired and unpaired comparison, and single and double correlation tests, Wilcoxon's matched-pair test, Spearman's correlation test and Mann Whitney's U-test were used. Differences with a probability level of $p > 0.05$ were considered non-significant (NS).

RESULTS

REVIEW OF THE PAPERS

CYCLOFENIL VERSUS PLACEBO IN PSS (I)

Twenty-seven of the 38 patients entering the study completed both six-month periods. Reasons for drop-outs were very high liver transaminases in three patients, cardiac death in two, and drug allergy, alcoholic problems, congestive heart failure, reactivation of tuberculosis, arteriosclerotic heart disease, and lethal progression of PSS in one subject each.

No death was attributed to the cyclofenil. Liver enzyme abnormalities were seen inl3 of 35 drug-periods, and in 5 of 30 placebo-periods. One patient who completed the study developed haemolytic anemia.

The patients were thoroughly investigated for signs of malnutrition. No significant correlation was obtained between esophageal involvement and different biochemical parameters, such as hemoglobine, cobalamine, folic acid, gastrine and fecal free fatty acids. No changes were detected in blood morphology, except for the patient with hemolytic anemia. Immunoglobulins and the complement factors C_3 and C_4 were within normal limits in almost all patients.

Serum creatinine and systemic blood pressure were normal and remained so in all patients during the study. Reduced Cr-EDTA clearance was seen in nine out of 38 patients. There were no significant differences in kidney function between the drug and the placebo periods. Cr-EDTA clearance did not correlate either to the esophageal function or to the static lung compliance.

Overall impairment was seen during 17 drug-periods and 9 placebo-periods (NS). A paired comparison of the status at the end of each treatment period resulted in the following distribution: 15 were improved after the drug-period and 4 at the end of the placebo-period ($p < 0.01$). Eight were unchanged. In patients with a disease duration of five years or less, joint stiffness and pain were less during drug treatment than during placebo treatment ($p < 0.05$). Esophageal peristalsis improved in the whole group ($p < 0.05$). Blood folate increased ($p < 0.01$). Working capacity was lower after the drug-period than after the placebo-period ($p < 0.05$). Other important parameters did not change significantly.

LUNG FUNCTION IN PROGRESSIVE SYSTEMIC SCLEROSIS (II)

The fundamental abnormality of lung function seen was a less compliant lung parenchyma. As a result, TLC, VC and ventilatory capacity were reduced. Impaired thoracic mobility also appeared to be of some importance. A mild intrinsic bronchial obstruction was found. In seven patients pulmonary resistance did not increase during a prolonged expiration, as it normally does. This was taken as a sign of increased bronchial wall rigidity. Very little impairment of gas exchange was found at rest. PaO_2 was slightly lower than normal at the highest work load. The only difference between smokers and non-smokers was a higher V_D/V_T among smokers. No correlation was found between static lung compliance and roentgenographic findings.

FACTORS LIMITING EXERCISE PERFORMANCE IN PROGRESSIVE SYSTEMIC SCLEROSIS (III)

Maximal working capacity was studied in 22 patients with PSS. Special attention was given the heart and lung function, joint mobility and muscular strength. Working capacity was on the average 51 % of the predicted normal value. Ventilation at maximal work load was high, despite normal arterial blood gases and presumably normal physiological dead space; this was probably due to an increased demand on ventilation from an increased muscular metabolism. The maximal heart rate was lower than had been predicted. Patients with low physical capacity had only a

small fall in base excess. One-third of the patients developed arrhythmia during exercise, which contributed to a low physical performance. Myocardial involvement, indicated by QRS changes in the ECG, was common. Myocardial fibrosis and scars can develop in PSS without clinical manifestations of infarction. There was no close linkage between heart dysfunction and lung fibrosis, or joint and muscle impairment. Impaired circulation, lung function and locomotive function appeared to contribute equally to a reduction of working capacity. At least two involved organic systems contributed to this reduction in almost all the patients.

EARLY CHANGES IN THE ESOPHAGEAL FUNCTION IN PROGRESSIVE SYSTEMIC SCLEROSIS (IV)

The characteristics of early esophageal dysfunction were studied with manometry and cine radiography in relation to clinical symptoms in 21 patients with PSS. Manometry was also performed in a matched control group. Mean resting pressures in the upper and in the lower esophageal sphincters were significantly decreased in PSS. Twelve patients (58 %) had no detectable peristalsis in the lower esophagus. The mean pressure amplitude of the peristaltic wave was found to be lower than normal in the upper esophagus in the group of patients with peristalsis. The only feature of esophageal dysfunction in some patients was an increased speed of the peristaltic wave in the middle and lower esophagus. This is interpreted as an impaired coordination of the propulsive peristalsis. Neuromuscular dysfunction of the esophagus in its full length was demonstrated in PSS. At cine radiography, 13 patients (62 %) had severe impairment of the peristaltic function in the distal two-thirds of the esophagus. Hiatal hernia was found in six patients. The esophageal scores based on manometry correlated well to those based on radiography ($p < 0.01$). A proper radiographic technique, including cine radiography of the recumbent patient, gives adequate information for clinical purposes. To detect and quantify early changes in the amplitude or speed of the propagation wave, manometry is necessary.

GENERAL DISCUSSION

PSS is an uncommon disease of unknown etiology. The extent of the disease can range from limited skin involvement to a generalized stage involving many organs. The time-course is not predictable. Spontaneous remissions are seen, as well as a rapid progression causing death within a few months. The prognosis depends upon the degree of involvement of the kidneys, heart and lungs. The modes of treatment attempted in different centres have mainly been intended to relieve the symptoms and complications of PSS, and probably have had little effect on the underlying pathogenesis of the disease about which our understanding is very limited. This study was started because no treatment has earlier been proven effective in properly controlled trials.

CYCLOFENIL TRIALS

Cyclofenil (bis(p-hydroxyphenyl)cyclohexylidenmethane) is a weak, non-steroidal oestrogen. It was developed in Sweden during the 1960's for the treatment of amenorrhoea and the induction of ovulation. It is registered and approved for these indications throughout Europe, and has been in clinical use about 13 years.

The theoretical basis for trying cyclofenil (Sexovid^{R}, Ferrosan AB, Malmö) in PSS patients was found in the experimental observations of Herbai (1971). In his studies to assess the capability of weak oestrogens to inhibit sulphate incorporation into cartilage, cyclofenil showed the greatest effect in relation to its oestrogenicity.

In an unpublished study on human dermal fibroblasts, high concentrations of cyclofenil in water solution were found to inhibit collagen synthesis (Harvey 1979, personal communication). Kjellström, Malmquist and Persson (1981) cultured fibroblasts from both normal subjects and PSS patients, and studied the effect of cyclofenil on the synthesis of collagen. They were not able to demonstrate any effect of cyclofenil. Cyclofenil in a solution with bovine albumine corresponding to clinical plasma concentrations was, however, found to inhibit the proteoglycan synthesis in

chondrocyte cultures (Mason & Black 1982). Proteoglycan is a constituent of collagen. The available information on cyclofenil's influence on collagen synthesis is not altogether clear, but gives a basis for possible therapeutic effects in PSS.

Five studies have been published on the use of cyclofenil in PSS. The first was a case report by Herbai (1974). As the results were judged to be positive, an open pilot study was conducted in six patients treated for 3 - 36 months with cyclofenil (Herbai, Blom & Boström 1977). This study also showed improved well-being and decreased skin tethering. The third paper reported improved pulmonary function in a patient treated with cyclofenil for twelve months (Blom-Bülow, Fridriksson & Herbai 1980).

The fourth published study was a multi-center open clinical trial in 29 patients (Blom-Bülow et al. 1980). This study also showed a clear effect on skin condition, regress of ulcerations, Raynaud's phenomenon, joint pain and stiffness. Most of the patients experienced an increased sense of well-being. No indication of effects on visceral involvement was found. The findings supported the positive observations of previous studies. It was, however, clearly stated that particularly in a disease such as PSS, with its varying clinical picture, firm conclusions can only be drawn from controlled studies. A double-blind cross-over study of cyclofenil versus placebo was therefore undertaken to evaluate possible therapeutic effects, and to investigate the side-effects of cyclofenil (I).

The high mortality and high frequency of drop-outs due to terminal-stage disease in the controlled study indicate that the material also included patients with very severe PSS. In particular, patients who had pulmonary fibrosis, renal damage or had lost much weight tended to drop out. It seems likely that several patients had reached a stage of advanced, irreversible disease, where positive effects of the drug would be difficult to ascertain.

Since renal failure is a serious sign in PSS and requires an aggressive treatment strategy, Cr-EDTA clearance should be performed early in the disease.

Observations in the open studies indicated that six months' treatment with cyclofenil would be a suitable period for evaluating effect of the

drug. Our present experience indicates that even longer periods of study are advisable. One reason is that beside direct drug effects, prevention of progression may occur. Possible drug-effects persisting into a following placebo period would, furthermore, be of less importance in the drug evaluation. Investigations with one year on each mode of treatment would also exclude seasonal variations.

The results of our study have initiated another double-blind trial of cyclofenil and placebo by Black et al. in England (1982). The design of their trial was an optional double-blind cross-over at 6 months, at which time it was decided if there was a positive effect of the given treatment. If not, the other treatment was given for 6 months. This resulted in 14 patients recieving cyclofenil and four placebo ($p < 0.05$) during the second period. Significant differences in response in favour of cyclofenil were: sclerosis and tethering of the skin, elbow movement and esophageal reflux. Five patients dropped out due to abnormality of liver function tests, and another three patients dropped out due to vomiting, depression and headache.

SIDE-EFFECTS OF CYCLOFENIL

A number of reports of abnormal liver function tests during cyclofenil therapy have been received by the Swedish Committee on Adverse Drug Reactions. In the PSS studies, several cases of elevated liver transaminases without jaundice have been reported. In a study of 41 male patients with cancer of the prostate using prolonged treatment with doses up to 3000 mg/day, five patients showed a slight elevation of serum bilirubin. Two of these had elevated transaminases. No severe degree of subjective feminization was seen, although the investigators observed four cases of objective feminization (Carstensen et al. 1969).

A recent study of the pharmacokinetics of cyclofenil has shown that its biological half-life is 29 ± 14 hours (Borgström 1981). Our administration of 200 mg three times daily may have caused the accumulation of too high and toxic concentrations in some patients, resulting in various unspecific side-effects (I). To see if the high frequency of abnormal liver function tests was caused by too high dosage, cyclofenil was given 300 mg daily for three weeks each month, followed by a week of placebo, in the study

performed by Black et al. (1982). This dosage was 50 % of that we used, but resulted in a similar frequency of high liver transaminases. The elevated liver enzyme values are reversible. Today, we recommend a single daily dosage of 300 mg cyclofenil in PSS treatment. Cyclofenil has not contributed to the mortality in our study.

A positive Coomb's test with hemolytic anemia during cyclofenil-treatment of scleroderma occurred in one of our patients (I). The anemia started during the first months of cyclofenil-treatment (Wollheim, Ljunggren & Blom-Bülow 1981). A similar complication has also been shown by Russell & Schacter (1981). French investigators have found a positive direct anti-globuline test in six women, 17-50 years old, on cyclofenil for gynecological reasons (Micouin et al. 1978). No information about the dosage, the duration of the treatment or the frequency of this finding was given. Cyclofenil has to be included among drugs capable of inducing immunological reactions such as positive Coomb's test and, in rare instances, haemolytic anemia.

The overall side-effects appear to be acceptable in PSS in relation to the prognosis of the disease. The alternative often proposed is treatment with D-penicillamine, which is a much more toxic drug.

PULMONARY MANIFESTATIONS

The typical lung morphology in PSS is a diffuse interstitial and alveolar fibrosis. This seems to be an early feature, also seen in patients with a short duration of disease. Measurement of static lung compliance may be a test that rather well expresses the degree of collagen involvement (II).

As in several earlier reports, we found decreased VC and TLC, which we attributed primarily to the low compliance of the lungs. We found that the PSS patients were not able to compensate for lung stiffness by creating highly negative pleural pressure at TLC, as most other patients with poorly compliant lungs do. Thoracic restriction and muscular insufficiency could thus be of importance, but secondary, for the reduced lung volumes in PSS.

We did not find any correlation between static lung compliance and roentgenographic findings, and conclude that chest roentgenography is of little value for evaluating parenchymal involvement in PSS. One must be critical towards many reports on lung fibrosis in PSS, where the degree of fibrosis is based on chest roentgenograms. It appears unjustified for bilateral basal fibrosis on chest roentgenograms to be one of the three minor criteria given by the American Rheumatism Association for the establishment of the PSS diagnosis.

Increased bronchial wall rigidity was shown in almost one-third of the patients. This finding is new and highly interesting. It has also been observed in our laboratory in cases with active sarcoidosis (II).

GAS EXCHANGE

Gas exchange, both at rest and during work, is remarkably normal in PSS (II). We did not find any patient with abnormal gas exchange who did not have an abnormal static lung compliance or VC. We therefore advise restriction with arterial punctures in these patients, who show a marked tendency to long-standing vasospasm. In patients where there is still a need for studying the gas exchange, the best information is probably obtained by measuring PaO_2 and $PaCO_2$ at maximal work. The sum of PaO_2 and $PaCO_2$ reflects the alveolar-arterial oxygen pressure difference in PSS.

PHYSICAL PERFORMANCE

All of the patients had a working capacity lower than that predicted (III). Circulation, lung function and locomotive function were found to be of nearly equal importance for the limitation of physical performance in PSS.

It is interesting that the PSS patients had a much higher ventilation in relation to work load than normal subjects. The changes in lung mechanics impede ventilation and increase the work of breathing. It is also reasonable to assume that impeded mobility of the locomotive organs reduces the total efficiency of the muscular energy turn-over. One might thus expect a high aerobic metabolism in relation to the work load, and an increased

need of ventilation that is difficult to maintain. This chain of events certainly contributes to the exertional dyspnoea seen in these patients.

Patients with the best working capacity had a fall in base excess similar to that of the healthy subjects, and reached a high heart rate at maximal work. This indicates that they were close to their aerobic threshold, which was a limiting factor for their working capacity.

Patients with a working capacity below 50 % of that predicted did not reach a high heart rate or a very low base excess. In this group, arrhythmia developing during exercise was the more important circulatory mechanism contributing to limitation of exercise capacity. Special attention must be paid to these arrhythmias, which are missed in a resting ECG. Two of the patients with exercise arrhythmias died suddenly of heart disease during the course of the study. Efforts to treat the arrhythmias should thus be done on the basis of proper diagnostic tests, e.g. exercise tests with ECG and long-term ECG recording.

MYOCARDIAL CHANGES

QRS changes of resting ECG are common in PSS, and myocardial fibrosis and scars may develop without clinical manifestations of infarction. It is not known if myocardial changes are secondary to vascular engagement, or are directly related to fibrotic degeneration of the myocardium. In future trials of PSS treatment, some interest should be focused on drugs with circulatory effects to evaluate possible protective actions on the myocardium. Drugs that show interesting vascular effects in PSS are prostaglandin E_1 (Martin & Tooke 1982) and calcium channel-antagonists, like nifedipine (Rodeheffer et al. 1983).

JOINT AND MUSCLE FUNCTION

Joint and muscle function was as important as lung and heart function for limitation of exercise capacity. Stiffness and pain from joints and muscles are particularly important in regard to the patient's subjective sense of well-being. It is therefore encouraging that cyclofenil had positive

effects on these symptoms. Symptomatic treatment and physiotherapy are important remedies for maintaining joint and muscle function.

ESOPHAGEAL FUNCTION

Esophageal dysfunction is a very common feature in PSS (IV). Reports on the esophageal function, based on barium swallow examination with the patient standing, may have given the false impression that the wall of the esophagus is stiff and non-compliant. The esophagus has sometimes been judged as being a rigid tube. Cine radiography with the patient recumbent showed that in many cases the loss of effective peristalsis in the distal part of the esophagus was accompanied by dilatation and delayed emptying. There was no impression of esophageal stiffness in any of the cine films, but rather of atony and flaccidity of the wall. These findings agree well with the histological features of the esophagus in PSS. Atrophy of the smooth muscle is the most common finding. In view of this, it is understandable that the esophageal pressure studied with the balloon technique gives an equally accurate measure of the pleural pressure in PSS patients as in healthy subjects (II).

Little attention has earlier been paid to the upper part of the esophagus, in which the muscle fibres are mostly of the striated type. Manometry showed that the mean resting pressure in the upper sphincter was significantly decreased. The pressure amplitude of the peristaltic wave in the upper part of the esophagus was clearly lower than normal. These observations of upper esophageal dysfunction were conclusive probably due to the direct comparison with the matched controls. In individual patients, however, esophageal dysfunction is more easily observed in the lower esophagus.

The only abnormal parameter in some patients was an increased speed of the peristaltic wave in the middle and lower esophagus. In some patients, the whole lower part of the esophagus contracted practically simultaneously. The abnormally high speed of the peristaltic wave signifies impairment of the coordination of the propulsive peristalsis. This phenomenon probably precedes a state of aperistalsis of the lower esophagus.

There were significant correlations between esophageal involvement and parameters related to striated muscle function. No significant corrrelation to lung fibrosis or to joint involvement was found. These findings suggest that esophageal dysfunction is more closely linked to neuromuscular function than to the fibrotic features of the disease.

The data gained from this study support the concept that the esophagus is involved in its full length, and that the cause of the dysfunction lies in the neuromuscular mechanisms.

The close correlation seen between the results of cine radiography and those of esophageal manometry in this investigation shows that a proper radiographic technique, which includes cine radiography with the patient recumbent, gives adequate information on esophageal function for clinical purposes. Manometry is suitable for research purposes, for detecting e.g. an increased propagation speed, or for quantifying esophageal function in relation to treatment.

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Cyclofenil versus Placebo in Progressive Systemic Sclerosis

A One-Year Double-Blind Crossover Study of 27 Patients

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ABSTRACT. Cyclofenil was evaluated versus placebo in the treatment of progressive systemic sclerosis (PSS, scleroderma) in a 2×6-month double-blind crossover study. The mean duration of disease was six years. Of 38 patients entering the study, 27 completed both periods. Reasons for drop-outs were very high liver transaminases in three cases, cardiac death in two, and drug allergy, alcoholic problems, suspected congestive heart failure, reactivation of tuberculosis, arteriosclerotic heart disease, and lethal progression of PSS in one case each. No fatality was attributed to cyclofenil. Liver enzyme abnormalities were seen in 13 of 35 active drug periods and in 5 of 30 placebo periods. Cutaneous and visceral involvement were assessed by a large battery of subjective parameters and objective tests. Overall improvement was seen during 17 drug periods and nine placebo periods (N.S.), but a paired comparison of the status at the end of each treatment period resulted in the following distribution: 15 were improved at the end of the drug period, four at the end of placebo period ($p<0.01$) and eight were unchanged. In patients with a disease duration of five years or less, joint stiffness and pain were less on drug than on placebo treatment ($p<0.05$). In the whole group, oesophageal peristalsis improved ($p<0.05$). Blood folate increased ($p<0.01$). Working capacity was lower after the drug period than after the placebo period ($p<0.05$). Several other parameters, however, did not change significantly. Cyclofenil appears to be a promising drug in the treatment of PSS and should be tested further in controlled long-term studies.

Key words: progressive systemic sclerosis, scleroderma, cyclofenil, controlled study, pulmonary function, oesophageal peristalsis, renal function, blood folate.

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Progressive systemic sclerosis (PSS) is a multisystem disease characterized by fibrosis and thickening of the skin. It also affects internal organs, particularly the oesophagus, heart, lungs, kidneys and intestines. The cause of PSS is unknown, but increased deposition of collagen is a prominent feature (21). The clinical course is varying and displays three stages: an oedematous, often preceded by years of Raynaud's phenomenon, an indurative, and an atrophic (21). A multitude of drugs—vasodilators, antihypertensives, hormones, immunosuppressive agents and others—have been tried in attempts to influence the disease, mostly in open and uncontrolled studies (9, 19). In open trials, penicillamine has been found to be effective against skin involvement (2, 15) but not against visceral symptoms. In one controlled study, colchicine was reported to reduce skin collagen (1), whereas N-acetylcysteine had no effect in another carefully controlled one-year placebo study (10).

In 1974 Herbai (13) published a case report showing apparently favourable effects of cyclofenil, a drug known to be a weak oestrogen but having a marked growth-retarding effect in animal studies (12). Encouraging results were reported later from open studies in a total of 29 cases (3, 14). It seemed therefore important to test this apparently rather untoxic drug in a controlled double-blind trial. Since the open studies had indicated that the onset of effect occurs after 2–4 months, a study over two six-month periods seemed appropriate. Because of the limited availability of suitable cases, a cooperative study with participation of centers in Lund-

Abbreviations: PSS = progressive systemic sclerosis, BP = blood pressure, TLC = total lung capacity, RV = residual volume, VC = vital capacity, ASAT = aspartate aminotransferase, ALAT = alanine aminotransferase, GT = gamma glutamyl transferase, ANA = anti-nuclear antibody.

Table I. *Clinical data on drop-outs and patients completing the study*

	Patients who completed the study		Drop-outs and withdrawals	
	N	%	*N*	%
No. of pats.	27		11	
Females	14		6	
Males	13		5	
Age (y.)	52±13		59±9	
Height (cm)	170±10		169±7	
Weight (kg)	65±16		60±11	
Duration of disease (y.)	6.3±5.7		6.9±4.5	
Raynaud's phenomenon	25	93	10	91
Sensitivity to cold	26	96	11	100
Chilliness	23	88[a]	6	67[b]
Skin tightness				
Hands	27	100	11	100
Other	27	100	10	100[a]
Skin ulcerations	14	52	8	67[b]
Interstitial oedema, hands	19	70	9	82
Teleangiectasis	13	48	7	64
Hyperpigmentation	9	33	4	36
Joint pain and stiffness	26	96	9	82
Dysphagia	14	52	6	55
Weight loss >10 kg before start of the study	6	22	5	45
Pulmonary fibrosis	6	22	6	55
Reduced Cr-EDTA clearance <80% of predicted at start of the study	4	14	5	45
Antinuclear antibody	14	52	6	55

Data missing on [a] one patient, [b] two patients.

Malmö and in Uppsala was organised. We report on 38 patients who entered the trial starting in April, 1977. The aim of this report is to give an overview of methods and results for the different organ systems which were examined. The patient series and the side-effects of cyclofenil are also reported. Further details regarding cardiopulmonary function, oesophageal function and peripheral circulation will be published later.

PATIENTS AND METHODS

Selection of patients

Patients from our clinics and others, who were referred to us, were included if they fulfilled the following criteria: typical sclerodermatous skin changes, a history of Raynaud's phenomenon or sensitivity to cold and at least one definite site of visceral involvement. Fully voluntary consent was obtained from all patients after having been informed about the investigation.

Patients who had been treated with chloroquine or immunosuppressive agents during the preceding six months were excluded. Continued low doses of cortisone were permitted, but the patients were told to keep the dose constant throughout the study. They were also permitted to continue previous intake of salicylates, indomethacin and paracetamol. Clinical features of the participants are presented in Table I. Sixteen women and 8 men entered in Lund–Malmö, 4 women and 10 men in Uppsala.

Design of the study

According to a double-blind crossover design, each patient was treated for six months with cyclofenil in a dosage of 200 mg three times daily (reduced to 200 mg twice daily in two women of 40 kg) and for six months with placebo tablets of identical appearance. The order of treatment was randomized and the tablets were marked with a code number which was kept secret until all data had been compiled and tabulated.

Assessments

A full clinical and laboratory evaluation was carried out in Lund and Malmö or in Uppsala at entry and at 6 and 12 months. Each patient was also seen by the referring doctor at 2, 4, 8 and 10 months for the purpose of answering standard questions and laboratory safety controls. The full evaluation aimed at determining the degree of involvement of various organ systems. The tests employed and the total number of patients in the various groups are listed in Table II.

Skin and joint function

Skin involvement recorded included ulcerations, finger or hand oedema, hair loss, pigment abnormalities and teleangiectasis. Mouth opening was measured as maximal distance between the front teeth. Impaired mimic function was recorded. Skin elasticity was measured with a suction-cup apparatus according to Bluestone et al. (5).

Hand function was assessed by standardized measurement of dorsal extension, volar flexion, supination, pronation and hand opening. Grip strength was measured as the mean of three maximal compressions of a blood pressure cuff inflated to 30 mmHg.

Peripheral circulation

Evaluation of peripheral circulation included assessments of the presence of Raynaud's phenomenon, implying at least a two-phase colour change in fingers or toes consisting of pallor, cyanosis and/or reactive hyperaemia in response to exposure to cold or emotion as determined by the patient's history or the physician's observations. Increased sensitivity to cold denotes a similar reaction to exposure to cold. Hand thermography and resting blood flow, measured by venous occlusion plethysmography and segmental measurement of peripheral finger blood pressure, were studied only in the patients from Lund–Malmö. The results will be published separately.

Lung and heart function

Pulmonary function tests included determination of total lung capacity (TLC), residual volume (RV) in a whole body plethysmograph, while vital capacity (VC) and forced expiratory volume in 1 sec were measured with a

Table II. *The various assessments and the total number of patients in each test*

Test	No. pats.
Subjective assessments	27
Skin involvement (ulcers, oedema, pigment abnormalities)	27
Mouth opening	27
Mimic function	27
Skin elasticity on hands[a]	9
Hand function; extension, flexion, supination, pronation	27
Hand opening	18
Grip strength	13
Hand thermography[a]	14
Venous occlusion plethysmography (hands)[a]	14
Segmental finger BP[a]	14
Systemic (arm) BP	27
Lung volumes	27
Lung elasticity[a]	15
Pulmonary resistance[a]	15
Arterial blood gases at rest and during exercise	14
Gas-exchange studies	14
ECG at rest and during exercise	27
Chest radiography and fluoroscopy	27
Oesophagus	
Radiography	26
Cineradiography	21
Manometry[a]	13
Upper gastrointestinal radiography	23
Xylose absorption test	23
Schilling test	20
Glomerular filtration rate	27

[a] Performed only in the Lund–Malmö series.

Bernstein spirometer. Elastic properties of the lung were assessed from oesophageal pressure at different lung volumes (16). Pulmonary resistance and arterial blood gases were measured at rest and during graded exercise. Arterioalveolar oxygen difference was determined by collecting expired air in a Douglas bag. Arterial oxygen was measured after breathing pure oxygen at rest.

ECG was recorded at rest and during exercise. Arterial arm blood pressure (BP) at rest was measured with a BP cuff. A standard chest radiography was performed. The diaphragmatic motility was determined by X-ray fluoroscopy.

Oesophageal and gastrointestinal function

Oesophageal function was assessed by recording symptoms of dysphagia and heart burn and by radiography of the oesophagus in the supine position and by cineradiography. The patients from Lund–Malmö also underwent oesophageal manometry.

Gastrointestinal function tests included assessment of symptoms such as weight loss, meteorism, diarrhoea or constipation. A routine upper gastrointestinal barium examination was also performed, as well as xylose absorption test and Schilling test. Serum gastrin and faecal fatty acids were measured and the body weight was recorded.

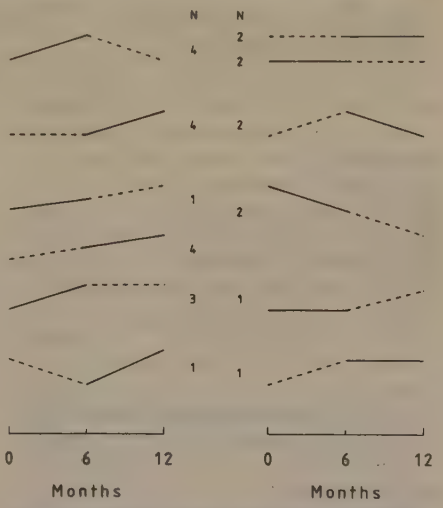

Fig. 1. Patterns of overall response in 27 patients. —= cyclofenil, ---= placebo. Rising line indicates improvement, falling line deterioration. The extent of these changes are not estimated or compared.

Renal function

Renal function was expressed in terms of serum creatinine and glomerular filtration rate measured by the ^{51}Cr- EDTA clearance technique (7).

Subjective assessments

Subjective criteria were used for assessing general well-being, feeling of chilliness, fatigue, headache, menstrual irregularities and sexual function.

Overall assessments

One and the same investigator (B. B.-B.) made an overall assessment of each patient based both on clinical data recorded in the charts and on interviews at 6 and 12 months. This allowed a classification of the evolution of the condition "within the period" as improved, deteriorated or unchanged by a comparison between the start and the end of the drug period or of the placebo period. It also allowed a classification "between periods" by describing the status at the end of the drug period compared to that at the end of the placebo period as better, worse or unchanged (Fig. 1).

Laboratory tests

The following laboratory tests were carried out: ESR, Hb, erythrocytes, WBC, platelet count, S-iron, cobalamines, folic acid, triglycerides, cholesterol, prothrombin, alkaline phosphatases, aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), gamma glutamyl transferase (GT), S-Na, S-K, S-Ca, U-Ca, S-phosphate, U-phosphate, S-Mg, U-Mg, S-uric acid, OH-proline excre-

Table III. *Drop-outs listed according to cause of withdrawal and stage of trial*
D = drug period, P = placebo period

	Months of treatment (crossover after 6 mo.)					
	0–2	3–4	5–6	7–8	9–10	11–12
Drug allergy	D					
High aminotransferases		D, D[a]			D	
Alcohol problems				D		
Suspected heart failure (fluid retention)			D			
Death from cardiac disease	D		P			
Arteriosclerotic heart disease (pacemaker)			P			
Tuberculosis				P		
Death from rapidly progressive disease		P				

[a] This patient also developed diabetes mellitus.

tion after gelatine-free diet for 2 days, S-albumin, orosomucoid, ceruloplasmin, IgG, IgA, complement factors C3 and C4 and anti-nuclear antibodies (ANA).

Statistical methods

The sign test, Wilcoxon's matched pairs tests and Spearman correlation test were used. All tests were one-sided (8). Differences with a probability level of $p>0.05$ were considered not significant (N.S.).

RESULTS

Adverse reactions and drop-outs

Table III shows the reasons for and the time of withdrawal of the 11 drop-outs. One patient was withdrawn due to an intestinal allergic reaction, which recurred after challenge by the drug. Three patients were withdrawn due to prominent aminotransferase abnormalities. After withdrawal of the drug the aminotransferases became normal but on rechallenge by the drug, in spite of reducing the dosage to half, they rose again to such an extent that we felt it unwise to continue. One patient, who developed a suspected congestive heart failure on cyclofenil, had a history of myocardial infarction. He had not received any diuretic treatment or digitalis for this condition. One patient with alcohol problems started drinking. One patient was withdrawn because of reactivation of pulmonary tuberculosis and another because of arteriosclerotic heart disease, which required implantation of a pacemaker.

Three patients, one of whom was on cyclofenil, died during the initial phase of the study. Two of these died from cardiac disease, one who had exhibited malignant arrhythmias during the exercise test and another in whom autopsy revealed signs of an old myocardial infarction. The third patient died from rapid deterioration due to PSS.

The remaining 27 patients completed the study according to the protocol.

Other recorded side-effects, which did not necessitate withdrawal from the study, were: haemolytic anaemia after drug therapy (1 case), transitory diarrhoea at the beginning of the drug period (2 cases), menstrual disorders after the drug period (4 cases) and after the placebo period (1 case), one woman reported increase in vaginal fluor during drug treatment and another during the placebo period. Eight of 13 men reported impotence at the start. The sexual function declined more during the placebo treatment in one of them and did not change during the following drug period. The others remained impotent during the entire investigation.

Table IV. *Number of side-effects/total number of patients in whom the reaction could occur*

	Drug period	Placebo period
High enzymes		
ASAT	10/35	3/30
ALAT	13/35	5/30
GT	6/28	2/29
Drug allergy	1/35	–
Fluid retention	1/35	–
Haemolytic anaemia	1/35	–
Diarrhoea	2/35	–
Menstrual disorders	4/14	1/14
Vaginal fluor	1/14	1/14
Impotence	–	1/15
Gynaecomastia	1/15	–
Breast tenderness (♂)	3/15	–

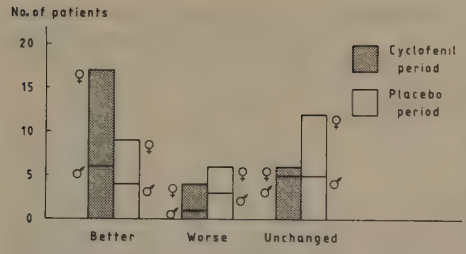

Fig. 2. Overall assessment of 27 patients after each treatment period.

One man reported gynaecomastia and another three reported early and transitory tenderness of the mammary glands. All side-effects observed are listed in Table IV.

Overall response

As shown in Fig. 1, various patterns of response could be distinguished on the basis of interviews and clinical data. Improvement within each period was noted after 17 drug periods and after nine placebo periods. Deterioration was seen within ten periods, four of which were drug periods (Fig. 2). The difference in evolution within drug and placebo periods was not significant.

A comparison of the state at the end of each treatment period resulted in the following distribution: 15 better at the end of the drug period, four better at the end of the placebo period, eight unchanged. The differences between the state at the end of the drug and placebo periods as judged by the doctor were significant ($p<0.025$). However, when the patients were asked about their treatment preference, 12 indicated preference for the drug, 12 for the placebo and three gave no preference. No correlation was found between drug preference and seasonal variations.

Joint function and skin symptoms

Patient preference with regard to subjective parameters is shown in Table V. For most parameters the majority of the patients did not report any difference between the drug and the placebo periods. A tendency in favour of the drug observed for joint pain and stiffness was not statistically significant.

The disease had lasted for five years or less in 17 patients. In this subgroup, joint pain and stiffness were significantly reduced after drug treatment ($p<0.05$). Measurements of hand function such as flexion, extension, supination and pronation did not change significantly after drug or placebo treatment. There was a positive correlation between the change in motion of the hands and the subjective assessments of joint stiffness ($r_s=0.57$, $p<0.01$).

The mean value of hand opening, measured in 18 patients, was after drug treatment 11.9 cm and after placebo treatment 11.3 cm ($p=0.06$). The mean value of grip strength, measured in 13 patients, was after drug treatment 154 mmHg and after placebo treatment 139 mmHg ($p=0.06$). Thus, both showed a tendency towards improvement after drug treatment.

Mouth opening did not change. The mimic function was better in five patients after the drug period and in three after the placebo period.

Skin elasticity was measured by suction cup in nine patients. There were no significant differences between the results from the two periods. A positive correlation was, however, found between the results from the "objective" measurements of skin elasticity and the subjective assessments of skin tightness on the hands ($r_s=0.78$, $p<0.01$).

Pulmonary and cardiac function

Chest radiography showed signs of pulmonary fibrosis in six patients and pleural changes in three. No significant changes were noted when the radiographic findings of the lungs or the motility of the

Table V. *Subjective assessments by patients completing the study*

Only patients who reported the symptom are included

	Improvement		
	On drug	On placebo	No change
Raynaud's phenomenon	6	5	14
Sensitivity to cold	3	5	18
Chilliness	9	4	10
Skin tightness			
Hands	11	6	10
Other	11	5	11
Skin ulcerations	6	3	5
Interstitial oedema, hands	6	3	10
Joint pain and stiffness	9	3	14
General well-being	7	2	5
Fatigue	6	5	11
Headache	1	2	1
Dysphagia	4	6	4

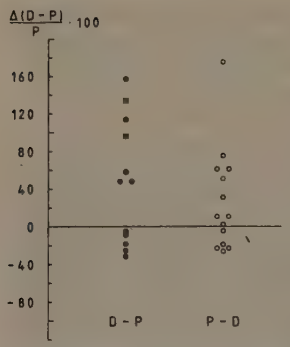

Fig. 3. Relative change (%) in blood folate levels in 26 patients. *D* = cyclofenil, *P* = placebo, *D–P* = patients first treated with drug, *P–D* = patients first treated with placebo.

diaphragm after the drug and after the placebo period were compared. In one patient, serial lung X-ray examination showed a marked reduction of subcutaneous calcinosis of the chest wall, starting during the initial (drug) period and continuing during placebo treatment.

Because of the high frequency of lung fibrosis among the drop-outs (Table I), only six patients with pulmonary fibrosis according to the static elastic pressure volume curves were left for the controlled study. Seven patients had a low VC (<80% of predicted normal) and only four had a reduced TLC (<80% of predicted). A high RV (>120% of predicted) was found in nine patients, some of whom had a normal pulmonary resistance. It appears that high RV and reduced VC may be due to reduced mobility of the thoracic wall. No significant differences were observed in lung elastic recoil or in lung volumes after the drug or the placebo treatment. Pulmonary resistance was elevated in four out of 15 patients. One of these four was smoker and another had given up smoking six years ago.

Unexpectedly, the blood gases were normal in most cases, not only during rest but also during exercise. There was no signicant difference between the drug and the placebo periods.

The mean value of working capacity measured by bicycle ergometry was 90 W after the drug and 95 W after the placebo. This difference is significant ($p<0.05$).

Eight patients had a pathological ECG at rest and another nine developed significant arrhythmias including high rates of supraventricular and ventricular extra systoles at work, but no difference was seen between the periods after drug and after placebo.

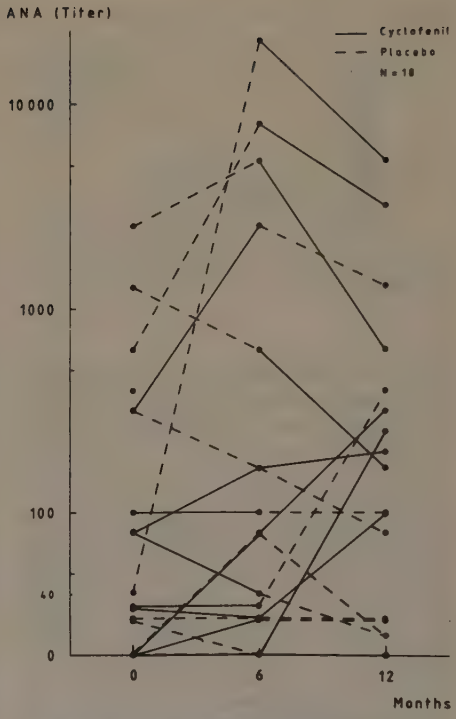

Fig. 4. Antinuclear antibodies in relation to treatment in 18 patients with at least one elevated level.

Oesophageal and gastrointestinal function

Oesophageal peristalsis was absent or decreased on cineradiography in nine out of 21 patients. No patient improved, two deteriorated during both drug and placebo treatment and another two only during the placebo period. One of three cases with gastro-oesophageal reflux improved after cyclofenil. Such changes in oesophageal function were seen only in early cases and they correlated well to subjective assessments. No statistically significant effects of drug were noted.

The more sensitive technique of oesophageal manometry showed improvement after drug treatment of the propagation rate of the peristaltic wave

Table VI. *Miscellaneous biochemical changes*

Mean values, range given in parentheses

	Initial level	After cyclofenil	After placebo	*p* (drug v. placebo)	Normal level
ESR (mm/h)	49 (4–77)	33 (5–126)	24 (4–67)	N.S.	2–30
S-haemoglobin (g/l)	133 (108–159)	131 (91–169)	132 (98–162)	N.S.	115–147 ♀ 131–163 ♂
S-albumin (g/l)	40.6 (31–57)	39.6 (33–48)	40.7 (33–46)	<0.05	40–52
S-orosomucoid (g/l)	0.87 (0.2–1.5)	0.80 (0.4–1.4)	0.90 (0.4–1.6)	<0.05	0.55–1.05
S-ceruloplasmin (g/l)	0.49 (0.40–0.75)	0.52 (0.35–0.88)	0.44 (0.25–0.72)	<0.05	0.22–0.48
S-Ca (mmol/l)	2.40 (2.20–2.70)	2.31 (2.10–2.50)	2.39 (2.25–2.50)	<0.05	2.2–2,6
U-Ca (mmol/l)	3.58 (1.0–7.0)	3.97 (1.1–10.0)	3.90 (1.4–8.8)	N.S.	2.5–8
S-Mg (mmol/l)	0.89 (0.73–1.06)	0.89 (0.77–1.04)	0.86 (0.70–1.05)	<0.05	0.7–1.1
U-Mg (mmol/l)	3.3 (1.2–9.0)	3.5 (1.5–7.1)	3.4 (1.3–5.2)	N.S.	2.5–7.5
S-ASAT (μkat/l)	0.40 (0.1–1.3)	0.60 (0.30–2.20)	0.39 (0.20–0.70)	<0.05	<0.67
S-ALAT (μkat/l)	0.27 (0.05–0.67)	0.63 (0.10–2.40)	0.35 (0.10–1.35)	<0.05	<0.67
S-ALP (μkat/l)	2.69 (1.3–4.9)	2.60 (1.0–5.0)	2.64 (1.4–4.2)	N.S.	<4.6
S-GT (μkat/l)	0.45 (0.11–2.00)	0.71 (0.06–3.8)	0.43 (0.09–2.90)	<0.01	<1.0
U-OH-proline (mmol/mol creatinine)	14.4 (5.6–28.9)	11.6 (1.6–22.3)	11.2 (4.6–22.4)	N.S.	–
Body weight (kg)	65.4 (43–114)	65.2 (42–109)	66 (43–115)	N.S.	–

in the lower part of the oesophagus. The mean propagation rate was 15.4 mm/s after drug treatment and 12.8 mm/s after the placebo period. The difference is significant ($p<0.05$). These studies were performed only on the patients from Lund–Malmö and will be reported separately.

Schilling test was normal in all but two patients when entering the study and did not change significantly during the two treatment periods. Six patients with subnormal xylose absorption test results had a mean value of 1.4 mg/ml/5 hours after the drug period and of 1.3 after placebo treatment (N.S.). The body weight did not change. Mean cobalamine level after drug was 342 pmol/l compared to a postplacebo level of 238 pmol/l (N.S.). All pretreatment folate levels were normal. The mean folate level after drug treatment was 37% higher than after placebo treatment (Fig. 3). The difference is significant ($p<0.01$).

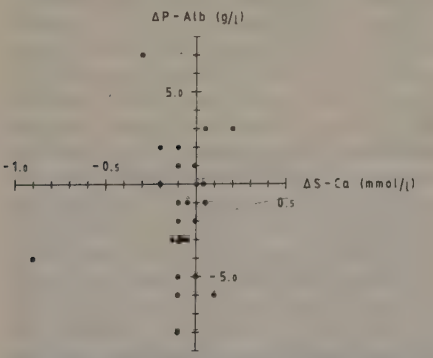

Fig. 5. Changes in serum calcium (*ΔS-Ca*) in relation to changes in plasma albumin (*ΔP-Alb*), expressed as differences between values after cyclofenil and after placebo.

Renal function

Serum creatinine and systemic BP were normal and remained so in all patients during the study and there were no significant differences between the drug and the placebo periods. The mean Cr-EDTA clearance after drug treatment was 89 compared to 85 ml/min per 1.73 m² after placebo treatment. The difference is not statistically significant.

Miscellaneous biochemical parameters

No changes were detected in blood morphology with the exception of one patient with haemolytic anaemia, who will be reported separately. No significant changes occurred in ESR. Immunoglobulins and complement factors C3 and C4 did not change.

ANA was present in 16 of 26 cases after drug treatment and in 15 of 27 after the placebo period. No significant pattern of change emerged (Fig. 4). Minor but significant falls in concentration were observed in albumin and orosomucoid (Table VI). Ceruloplasmin increased slightly. Serum-Ca was lower and serum-Mg higher after cyclofenil than after placebo (Table VI). The fall in calcium was not correlated to the fall in plasma albumin (Fig. 5).

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LUNG FUNCTION IN PROGRESSIVE SYSTEMIC SCLEROSIS

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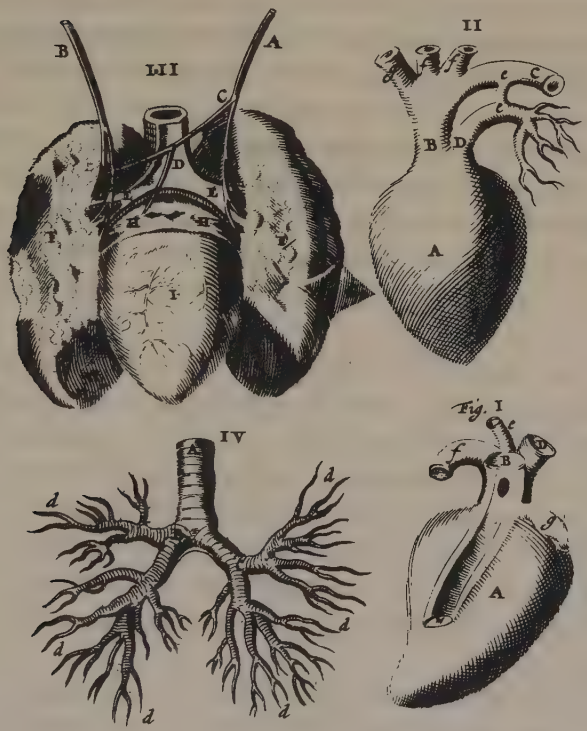

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ABSTRACT

Pulmonary function was investigated in 24 patients with progressive systemic sclerosis. The lung volumes were measured by a body plethysmograph. Bronchial and parenchymal properties were studied by relating pulmonary resistance and lung volume to pulmonary elastic recoil pressure. Pulmonary mechanics and arterial blood gases were studied during graded exercise on a bicycle ergometer. Arterial pO_2 was measured during pure oxygen breathing and physiological dead space was measured. The most fundamental abnormality appeared to be a less compliant lung parenchyma. This factor may explain lower TLC, VC and ventilatory capacity. A mild intrinsic bronchial obstruction was found. Seven patients showed signs of increased bronchial wall rigidity. Very little impairment of gas exchange was found at rest. PaO_2 was slightly lower than normal at the highest work load. The only difference between smokers and non-smokers was a higher V_D/V_T among smokers. No correlation was found between static lung compliance and roentgenographic findings.

In progressive systemic sclerosis (PSS, scleroderma), increased deposition of collagen affects many organs, such as the esophagus, heart, lungs, kidneys, intestines and the skin. Pulmonary involvement has been reported in a vast majority of cases (Piper & Helwig 1955; D'Angelo et al. 1969). At an early stage, capillary congestion and increased cellularity of the alveolar wall are seen. Later, fibrosis within the alveolar walls causes reduction of the lumen, and even obliteration of alveoli and alveolar capillaries (Sackner et al. 1964). There is also bronchiolitis with peribronchial fibrosis (Guttadauria et al. 1977). Fibrous pleuritis and pleural adhesions are common. Chest radiograph may be normal or show varying degrees of parenchymal changes similar to those observed at other diseases with interstitial fibrosis and pleural thickening (Colp, Riker & Williams 1973).

There is a poor correlation between clinical signs, respiratory function and radiological findings (Gondos 1960; Tuffanelli & Winkelmann 1961; Adhikari et al. 1962; Bianchi et al. 1966). In most cases, respiratory symtoms are preceded by articular or cutaneous manifestations of the disease, but occasionally they can herald its onset.

At an early stage, the interstitial inflammatory response and, later, indurative fibrosis cause reduction of pulmonary compliance and restrictive lung disease (Campbell & LeRoy 1975). Ventilation-perfusion inequality could be caused by obliteration of the pulmonary vascular bed. Wilson, Rodnan & Robin claimed in 1964 that the diffusing capacity for carbon monoxide may be impaired early in the disease. A reduction of the transfer factor may occur with or without a reduction in lung volumes (Bagg & Hughes 1979), or an increase in static elastic recoil pressure (Bjerke et al. 1979).

The aim of this paper is to describe the pulmonary function in PSS patients by using techniques which give information that is specific for the airway properties and mechanical characteristics of the lung parenchyma, and what consequenses this will have on physical activity. We also studied arterial blood gases at rest and at maximal effort. Twenty-four patients were investigated in Lund as a part of a major study of PSS (Blom-Bülow et al. 1981).

MATERIAL AND METHODS

MATERIAL

The patients fulfilled the criteria of PSS according to the American Rheumatism Association (Masi et al. 1980). They had typical scleroderma, all but one had Raynaud's phenomenon and all had involvement of at least one visceral organ (Table 1).

Fully voluntary and informed consent was obtained from all of the patients. The study was approved by the Ethical Committee of the University of Lund.

Twenty-four patients were studied, 16 women and eight men. The mean age was 49 years (range 23-72). The average duration of the disease was six years (range 1-17). There were 13 lifelong non-smokers. The average tobacco consumption was in 4 smokers 18 pack years, and in seven ex-smokers 13 pack years. In the further discussion, the smokers will also include the ex-smokers.

Table 1. Clinical findings in the patients.

	n	% of patients
Females	16	67
Males	8	33
Smoker/ex-smoker/non-smoker	4/7/13	
Raynaud's phenomenon	22	92
Skin tightness	24	100
Skin ulcerations	11	46
Joint stiffness	24	100
Weight loss $\geq$ 10 kg	8	33
Dysphagia	14	58
Antinuclear antibody	14	58

VENTILATORY CAPACITY AND LUNG MECHANICS

Vital capacity, VC, and forced expiratory volume in 1 sec, FEV_1, and $FEV_1/VC \times 100$, FEV%, were measured with a Bernstein spirometer. Total lung capacity, TLC, residual volume, RV, and functional residual capacity, FRC, were measured with a body plethysmograph (Jonson 1969a). When the patient was breathing against a closed valve for determination of thoracic gas volume the breathing frequency was kept at about 0.5 Hz.

A 10 cm long esophageal balloon was used for measurements of pulmonary resistance, R_L, and static elastic recoil pressure, Pel_L. R_L at rest was measured through expirations covering most of the vital capacity at a standardized flow rate of 1 ℓ/s. R_L was related to the simultaneously measured Pel_L. Pel_L was determined during flow interruptions with a duration of 0.35 s that occurred every 0.7 s during the full expiration. The resulting curve, R_L versus Pel_L, Fig. 4, displays information that is intended to specifically illustrate changes of intrinsic bronchial properties. The flow regulator method that we used and its application in healthy and diseased subjects have been described earlier (Jonson 1969a; 1969b; 1970a; 1970b).

The pulmonary static elastic pressure volume, P/V, curve was determined in a body plethysmograph similar to that previously described (Jonson 1969a). The patient inspired maximally twice before a long expiration through a flow regulator. This limited the flow to 1 ℓ/s and closed the airway at intervals of about 0.3 s. During the periods of no flow, Pel_L was determined. After the expiration, the patient returned to about his FRC. The airway was then shut by the flow regulator, against which the patients then made inspiratory and expiratory efforts for the determination of thoracic gas volume. The static elastic pressure volume diagram was then constructed from the spirogram, the transpulmonary pressure and the thoracic gas volume. Compared to the method previously described (Jonson 1969a), the patient did not have to inspire to a reproducible TLC value in order to align the pressure volume curve along the volume axis. Static lung compliance, Cst_L, was measured over the interval of the PV curve at 5-15 cm H_2O.

All calculations of static lung volumes, of R_L, and of the pressure volume curve were done by a computer (PDP 8I) that was connected on line to the

various transducers. The computer also controlled the electronic flow regulator from a Servo ventilator (Ingelstedt et al. 1972) that replaced the mechanical model used in previous studies (Jonson 1969a; 1969b).

Pulmonary mechanics were studied during a graded exercise test, during which flow at the airway opening, $\dot{V}$, was measured with a Fleisch pneumotachograph and transpulmonary pressure, P_L, with the esophageal balloon. Data were read 100 times/s by the computer during a period of up to 12 s comprising a number of complete respiratory cycles. Ventilation, $\dot{V}_E$, was calculated as:

$$\dot{V}_E = \frac{\Sigma \dot{V}}{2n} \qquad \text{(Eq. 1)}$$

n is the number of readings during the period. The factor 2 accounts for the reading of both expiration and inspiration. Tidal volume, V_T, was obtained from $\dot{V}_E$ and frequency. Dynamic pulmonary compliance, $Cdyn_L$, was measured from:

$$Cdyn_L = V_T \times (P_{L_E} - P_{L_I})^{-1} \qquad \text{(Eq. 2)}$$

in which P_{L_E} and P_{L_I} represent average transpulmonary pressure at the end of expiration and at the end of inspiration, respectively.

During complete respiratory cycles the mechanical energy taken up and dissipated as heat in the lung is related to pulmonary resistance. By measuring the energy taken up per time unit in the lungs and relating this measure to $\dot{V}_E$, average pulmonary resistance during exercise was calculated according to the principles given by Otis et al. (1956). This resistance value was called functional pulmonary resistance, Rf_L, by Ahlström and Jonson (1974).

TRANSMISSION OF PLEURAL PRESSURE TO ESOPHAGUS

To assess the transmission of pleural pressure to esophagus, the patient was allowed to make expiratory and inspiratory efforts against a closed valve. During this period, the pressure changes in esophagus were related to

the pressure changes at the airway opening. In accordance with the principles of our laboratory the pressure changes in esophagus should not differ more than 5 % from those recorded at the airway opening. It was not more difficult to find a balloon position with such an adequate pressure transmission in PSS patients than in other groups of patients.

It was considered possible that esophagus might be stiffer than normal in PSS and cause an artefact in the pressure level recorded. This was studied by inflating the balloon to various volumes under determination of average esophageal pressure at rest. This test showed that the esophageal pressure did not change more with varying degree of balloon inflation than in normal subjects or in patients with obstructive disease or with restrictive disease other than PSS (Table 2).

Esophageal disease in PSS does not affect the validity of esophageal pressure as a measure of pleural pressure.

Table 2. Change in esophageal pressure (ΔP) caused by a change in esophageal balloon gas volume from 0.5 ml. PSS patients were compared to groups of subjects that were healthy or had pulmonary disease of restrictive nature (mainly sarcoidosis) or obstructive lung disease. No significant difference between the groups were observed.

Balloon volume, ml	ΔP ± standard error of the mean, cm H_2O			
	PSS patients n=16	Healthy subjects n=14	Restriction n=21	Obstruction n=8
0.5 → 0.3	-1.7 ± 0.4	-2.0 ± 0.5	-1.9 ± 0.3	-1.3 ± 0.3
0.5 → 1.0	1.5 ± 0.4	2.1 ± 0.3	1.5 ± 0.2	1.2 ± 0.6
0.5 → 1.5	2.3 ± 0.4	2.9 ± 0.3	2.4 ± 0.2	1.9 ± 0.4

GAS EXCHANGE

Arterial blood was drawn from an indwelling catheter in the brachial artery and analyzed for blood gases with an automated analyzer (Instrumentation Laboratory 613) immediately after sampling. The oxygen saturation of hemoglobin was then calculated from the arterial P_{O_2} (PaO_2), pH and base excess.

Physiological dead space at rest, V_D, was calculated from composition of mixed expired gas (Scholander analysis) and from average $PaCO_2$ determined in 5 samples drawn during the collection period. PaO_2 was measured during pure oxygen breathing in order to estimate intrapulmonary shunt ($\dot{Q}s/\dot{Q}t$) from the equation given by Linderholm (1959) (PO_2 is given in kPa):

$$\dot{Q}s/\dot{Q}t = 100/(1 + 176/(P_AO_2 - PaO_2)) \qquad \text{(Eq. 3)}$$

P_AO_2 is the alveolar P_{O_2}. This was considered to equal atmospheric pressure less $PaCO_2$ and the pressure of saturated water vapour at 37°C.

The exercise test was done on a bicycle ergometer. After 4 min, an arterial blood sample was taken. Pulmonary mechanics was then measured. The load was stepwise increased until symtom limitation or until observations of heart arrhythmia from an electrocardiogram indicated cessation of exercise.

STATISTICAL METHODS

Student's t-test for paired and unpaired comparisons, single and double correlation tests were used for statistical analysis (Snedecor 1956). Differences with a probability level $p < 0.05$ are marked with *, $p < 0.01$ with ** and $p < 0.001$ with ***.

PREDICTED NORMAL VALUES

Most of our results are reported in per cent of predicted values in order to account for variations of sex, age, height, weight, etc. This mode is expressed by the suffix %p, e.g. VC %p.

VC, FEV_1, TLC, RV and FRC were predicted according to Berglund et al. (1963) and Grimby & Söderholm (1963). To predict normal pressure volume (P/V) curves, data of Jonson (1970a) and Knudson et al. (1978) were combined after personal communication with the latter. Data on $Cdyn_L$, R_L, Rf_L and static transpulmonary pressure at TLC (Pel_{TLC}) refer to a material of healthy subjects examined in this laboratory.

Predicted values of PaO_2, arterial pCO_2 ($PaCO_2$), alveolo-arterial oxygen pressure difference ($\Delta AaPO_2$), V_D/V_T and PaO_2 after 100 % oxygen breathing were obtained from Malmberg (personal communication; Malmberg, Fridriksson & Hedenström 1981).

Individual values outside the 95 % interval of confidence, corresponding to 1.96 SD, are classified as abnormal.

RESULTS

COMPARISON BETWEEN THE SMOKING AND THE NON-SMOKING PATIENTS

Smokers and non-smokers did not differ with respect to sex, age and duration of disease. Except for a significantly higher V_D/V_T in smokers, no differences in lung function or gas exchange were observed (Table 3). All patients will therefore be treated as a single group in the following presentation.

ELASTIC PROPERTIES OF THE LUNGS AND RELATED PARAMETERS

The pressure volume curves show that, at low values of Pel_L, the lung volumes fell within the normal range in all patients (Fig. 1). At higher values of Pel_L, the volumes tended to be reduced. The most conspicious abnormality of the pressure volume curve was, hence, the slope of the P/V curve, i.e. Cst_L. No patient showed a shift of the whole curve towards higher values of Pel_L, as is sometimes observed in other kinds of pulmonary fibrosis.

Table 3. Comparison between smokers and non-smokers. The only significant difference was a higher V_D/V_T %p in the smokers compared to the non-smokers ($p < 0.05$).*

	Smokers	Non-smokers
Number	11	13
Sex (M/F)	4/7	4/9
Age (years)	49	51
Duration of disease (years)	5.6	6.2
Skin ulcerations	6	5
TLC %p	90	88
VC %p	87	85
RV %p	112	108
FEV_1 %p	90	91
Cst_L %p	64	64
R_L %p	172	179
V_D/V_T %p[1)]	117*	97
PaO_2 %p at rest[2)]	95	93
PaO_2 at rest (kPa)[2)]	11.0	11.8
PaO_2 at maximal work (kPa)[3)]	10.9	11.8
PaO_2 after breathing pure oxygen (kPa)[2)]	71	71

1) n=8 for smokers

2) n=8 for smokers, n=12 for non-smokers

3) n=8 for smokers, n=11 for non-smokers

Dynamic compliance, $Cdyn_L$, measured during exercise, showed a fair correlation to Cst_L, particularly at the highest work load (Table 4).

The reduction of TLC to 81 % of that predicted, of VC to 86 %, and of FEV_1 to 91 % were statistically related to the decrease in Cst_L ($p < 0.01$, Table 4, Fig. 2).

There was no correlation between reductions in TLC and Pel_{TLC}. Pel_{TLC} was on average 92 % of that predicted. It was not abnormal in any single patient.

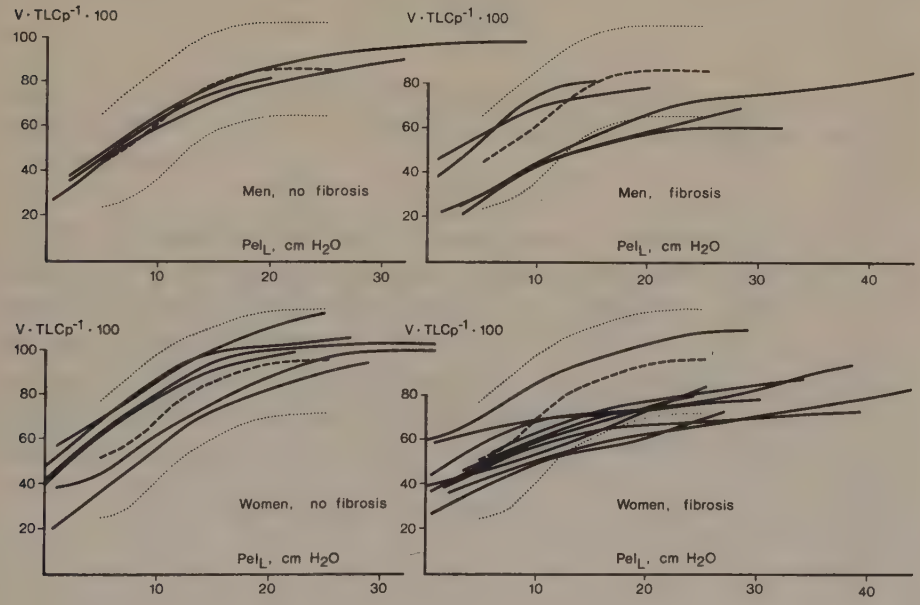

Fig. 1. The individual static pressure volume curves. The patients are defined as having no fibrosis (left panels) or having fibrosis (right panels), judged from the curves shown and from the dynamic P/V curves obtained during maximal work. The broken line shows the expected curve for a 50-year old person. The normal range is indicated by dotted lines.

*Table 4. Pulmonary function data in PSS. The number of abnormal cases in each parameter is given. Significant differences of a mean from predicted values and a correlation coefficient (r) indicating a relationship to Cst_L %p are indicated as: * $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$. $y = a + bx$, where $x = Cst_L$ %p.*

y	Mean	SD	Range	Relationship to Cst_L %p a	b	r	Number of abnormal cases below 1.96 SD	above 1.96 SD
Cst_L %p	64***	21	15-96	-	-	-	11	
$Cdyn_L$ %p at rest	66***	21	38-109	3.09	0.52	0.53*	3	
$Cdyn_L$ %p at maximal work	85*	30	42-140	18.8	1.00	0.72**	5	
TLC %p	89**	15	60-115	65.0	0.38	0.55**	5	
VC %p	86**	19	64-115	43.6	0.66	0.77**	9	
RV %p	110	29	58-154			-0.08		3
FRC %p	107	21	59-151			0.24	2	1
FEV_1 %p	91*	20	59-118	45.5	0.71	0.78**	5	
FEV_1/VC x 100 %p	104	17	89-146			0.08	6	5
R_L %p	176***	97	89-500			-0.27		8
Rf_L %p	114*	24	67-167			-0.28		3

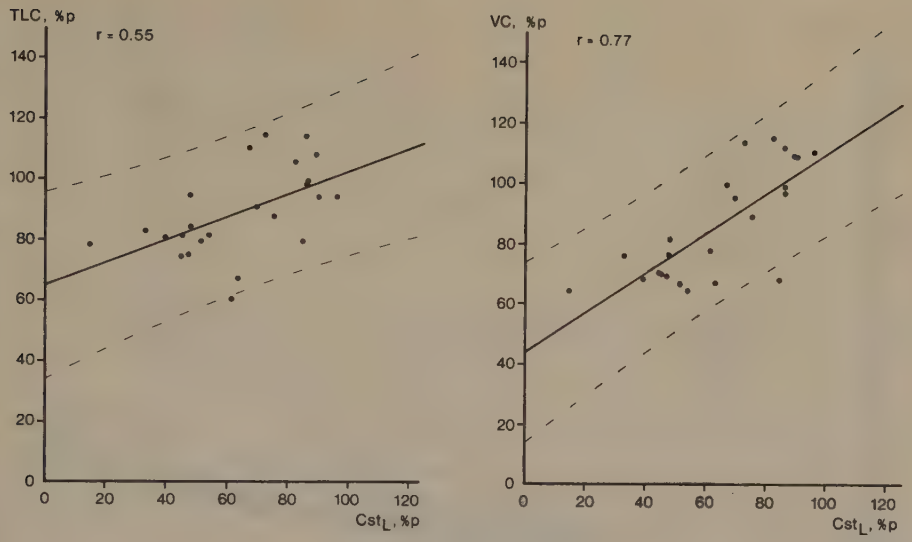

Fig. 2. The correlations between Cst_L %p and TLC %p (left panel) and VC %p (right panel) ($p < 0.01$). Interrupted lines show the 95 % confidence limits of the observations.

At chest radiography, eight patients were judged to have interstitial fibrosis, four of them also had pleural changes. Another four had only pleural involvement. Patients with very low Cst_L often had a normal radiograph. Four patients were judged to have fibrosis on the chest radiograph, but had a Cst_L within the normal range. In three of them, pleural changes were observed. There was no correlation between the radiographic findings and Cst_L (Fig. 3).

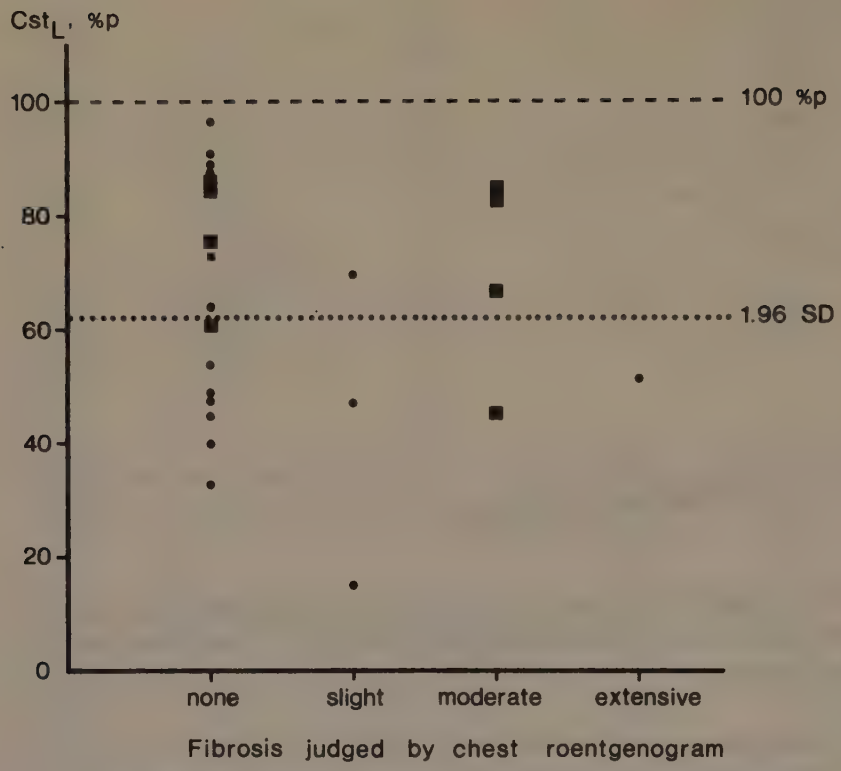

Fig. 3. The relationship between Cst_L %p and lung fibrosis judged by roentgenogram. The evaluations slight, moderate or extensive fibrosis refer to the interstitial changes in the lung parenchyma. ■ *indicates also pleural changes.*

INTRINSIC BRONCHIAL OBSTRUCTION AND RELATED PARAMETERS

Pulmonary resistance, R_L, was on the average 176 % of the predicted value at a Pel_L of 7.5 cm H_2O. It was significantly increased ($p < 0.001$). The normal range is wide, and only eight subjects had an abnormally high R_L.

A particular feature was observed in seven patients in the R_L versus Pel_L curves. The curves did not show the steep rise at Pel_L values below 5 cm H_2O that is regularly observed in normal subjects (Fig. 4; Jonson 1970a).

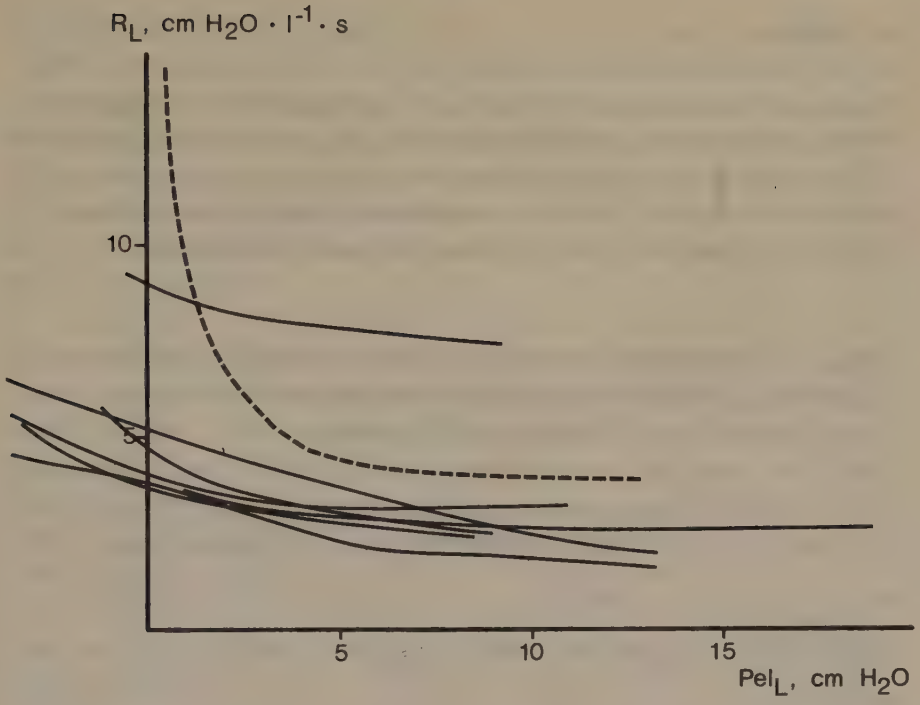

Fig. 4. Pulmonary resistance versus Pel_L in seven cases, in which the airways did not collapse despite nearly atmospheric pleural pressures. The dotted line shows the normal curve from another PSS patient.

Pulmonary functional resistance, Rf_L, measured at the highest work load, was on the average 114 % ($p < 0.05$).

R_L or Rf_L showed no significant correlation to Cst_L, to RV or to FEV%, all in % of predicted value.

On the average, FEV% was 104 % of that predicted. RV %p was 110 %. Both were within normal ranges.

GAS EXCHANGE

In three patients, no arterial blood gases were obtained. Two of these had advanced disease with a low Cst_L. The average PaO_2 at rest was not significantly lower than the predicted normal. No patient fell outside the 95 % interval of confidence (Table 5). One severely overweight patient had a PaO_2 and an oxygen saturation at rest at the lower normal limits.

*Table 5. Gas exchange at rest and at maximal work load. Significant differences of the mean from predicted value are indicated as: * $p < 0.05$ and ** $p < 0.01$. For predicted data n = 50.*

	Observed data			Predicted data	
	n	Mean	SD	Mean	SD
PaO_2 at rest (kPa)	21	11.3	1.28	11.6	1.71
PaO_2 at max. work (kPa)	19	11.4**	1.08	12.3	1.10
$PaCO_2$ at rest (kPa)	21	4.5*	0.44	4.8	0.63
$PaCO_2$ at max. work (kPa)	19	4.3*	0.57	4.7	0.60
$\Delta AaPO_2$ supine at rest (kPa)	21	2.7**	1.15	2.1	0.95
PaO_2 after breathing pure oxygen (kPa)	20	71**	8.0	75 [1)]	4.3
$\dot{Q}s/\dot{Q}t$ at rest supine (%)	20	9.4**	3.63	7.5 [1)]	2.10
V_D/V_T	21	0.33	0.10	0.32	0.09

1) Predicted data corrected for age were not available, see text.

The $\Delta AaPO_2$ was on the average 2.7 kPa, i.e. slightly, but significantly, higher than expected (Table 5). Only two cases had abnormal values, one of these was the overweight subject. The PaO_2 during pure oxygen breathing was on the average 71 kPa. In the normal material examined by Malmberg et al. (personal communication), the mean value was 75 kPa. Since our patients are somewhat older than those of Malmberg, the two materials are not strictly comparable. The same is true for the calculated $\dot{Q}s/\dot{Q}t$. V_D/V_T was found to be normal.

Maximal working capacity was on the average 51 % of the predicted normal (Blom-Bülow, Jonson & Brauer 1983, III, see page 65). PaO_2 was at maximal work 11.4 kPa, which is significantly lower than the predicted normal. In one patient, PaO_2 fell to 10.4 kPa, which was below the normal range when his $PaCO_2$ of 2.9 kPa was taken into account. Another patient fell to 8.7 kPa. He was the only one who fell significantly in calculated oxygen saturation during maximal work.

There was no significant correlation between the data on gas exchange and Cst_L, R_L or Rf_L.

There was, however, a significant correlation between $\Delta AaPO_2$ measured at rest and the sum (PaO_2 + $PaCO_2$) at rest, as well as PaO_2 after pure oxygen breathing (Fig. 5).

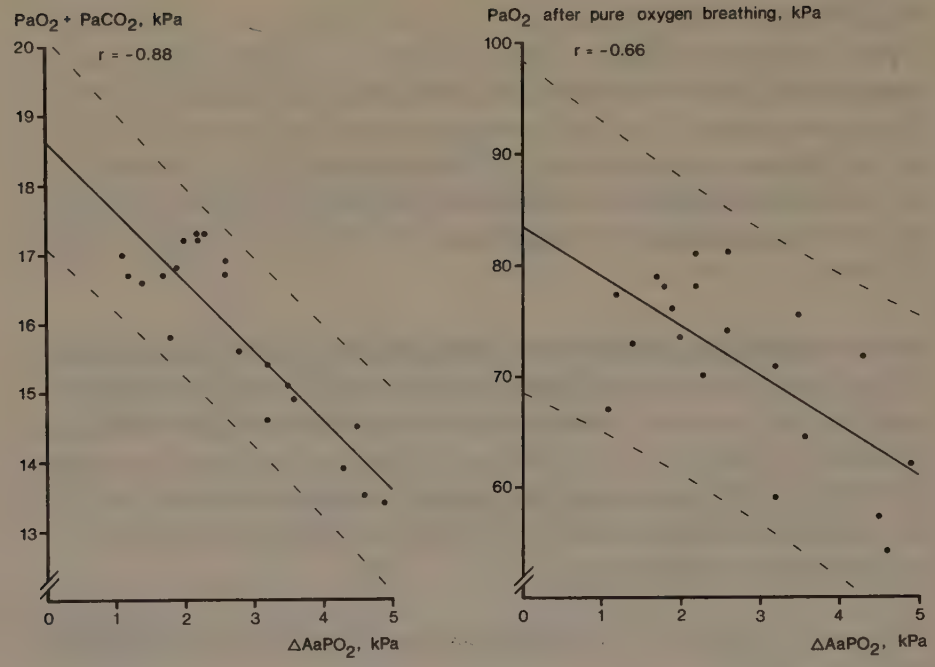

Fig. 5. The correlation between $\Delta AaPO_2$ and the sum (PaO_2 + $PaCO_2$) at rest and PaO_2 after breathing pure oxygen (PaO_2 100 %) ($p < 0.01$). $\Delta AaPO_2$ = 14.98 - 0.77 (PaO_2 + $PaCO_2$). $\Delta AaPO_2$ = 18.44 - 0.22 PaO_2 100 %. Interrupted lines show the 95 % confidence limits of the observations.

DISCUSSION

As esophageal disease is common in PSS the use of esophageal pressure as a measure of pleural pressure was examined with care. If the PSS patients had a stiffer than normal esophagus, the influence on the measured pressure of the volume of the esophageal balloon would be greater than in normal subjects and in other patients. Our data show no such difference. The transmission of pressure changes in the respiratory system to esophagus was also normal. Morphological studies show that atrophy of the esophageal muscular tissue is a dominant feature of PSS in this organ. Fibrosis is slight and apparently of secondary nature (Treacy et al. 1963; D'Angelo et al. 1969). On the basis of these observations it is not surprising that esophageal pressure appears to be as valid for estimation of pleural pressure in PSS as it is in normal subjects (Milic-Emili et al. 1964).

Changes of lung morphology in PSS are predominantly a diffuse interstitial and alveolar fibrosis. It is likely that most of our patients had fibrotic changes in the lungs. All patients had a static lung compliance lower than that predicted and 11 out of 24 patients had abnormal Cst_L. The decrease in VC and TLC has been reported earlier (Adhikari et al. 1962; Demuth et al. 1968; Guttadauria et al. 1977). We found that the dominating reason for reduced lung volumes is a low Cst_L. However, most patients with poorly compliant lungs due to other causes than PSS can partly compensate for lung stiffness by creating highly negative pleural pressure at TLC, i.e. a high Pel_{TLC}. The fact that our patients did not produce higher Pel_{TLC} than normal subjects shows that they did not use this compensating mechanism. Thoracic restriction then appears to be of some but secondary importance for low lung volumes in PSS, as was suggested by Hutås et al. (1973). We cannot judge whether the contribution from thoracic restriction was due to muscular insufficiency or to thoracic rigidity. The present results strongly indicate that static lung compliance is the factor that gives earliest indication of impaired lung function in PSS, and that most other functional deficits are of secondary importance.

Seven patients with fibrosis judged from static lung compliance had a normal chest roentgenogram. Three out of four patients with Cst_L within normal limits were assumed to have a moderate fibrosis on the basis of

the chest roentgenogram. These patients also had pleural involvement, which may have led to an overestimation of fibrosis (Fig. 3). Roentgenography appears to be of little value in the estimation of pulmonary parenchymal involvement in PSS.

There are fibrotic changes in peribronchial areas and bronchial walls presenting as small airway disease in function tests (Guttadauria et al. 1977). Our data on pulmonary resistance versus recoil pressure, are compatible with a mild airway obstruction due to such morphological changes. It is also possible that increased viscous resistance of pulmonary tissues contributes to the increase of pulmonary resistance.

The particular flat pattern observed in some R_L/Pel_L curves indicates that a majority of airways do not collapse at pleural pressures close to atmospheric conditions as they do in normal subjects. This is probably due to an increased bronchial wall rigidity that could well explain why PSS patients so seldom show atelectasis compared to matched controls (D'Angelo et al. 1969). This pattern has, in this laboratory, also been observed in cases with active sarcoidosis (unpublished observations).

Another consequence of the rigid bronchial wall is the difficulty in judging the relevance of FEV in % of VC, FEV%, in these patients. It will be influenced both by the rigid bronchial wall with its reduced compressibility and by obstruction of the airway. Changes in Pel_L will also affect FEV% (Jonson 1970b).

Blood gas values at rest, and during work, were remarkably normal. Impaired gas exchange was not an important factor for limitation of working capacity.

$\Delta AaPO_2$ measurements by collecting expired gas in a Douglas bag require technical equipment and are time-consuming. We found a good correlation between $\Delta AaPO_2$ and the sum ($PaO_2 + PaCO_2$) measured at rest. This sum seems to be useful for estimation of $\Delta AaPO_2$, at least in PSS.

PaO_2 did not rise during exercise in the way expected. The decrease seen in a few patients was moderate, and did not signify any alveolar-capillary block of functional importance. We could not confirm low oxygen saturation

at exercise in spite of "normal" mechanics of breathing, as reported by Wilson et al. (1964).

We did not, unfortunately, have access to the technical equipment for measuring the transfer factor or so-called diffusing capacity in our patients.

Several authors, using various methods, claim that the diffusing capacity of the lung (D_{LCO}) is the earliest and most sensitive test for detecting lung function impairment in PSS (Adhikari et al. 1962; Wilson et al. 1964; DeMuth et al. 1968; Bagg & Hughes 1979). Wilson et al. based their statement on D_{LCO} by using an unspecific method with great inter-individual variance in testing D_{LCO}. It is notable that two of their patients with the best values for D_{LCO} had a significantly low oxygen saturation at exercise and that some patients with extremely low D_{LCO} had normal saturation both at rest and at exercise. They furthermore used $Cdyn_L$ measured at rest to define elastic properties of the lungs, which is a poor method. Of our eleven patients with abnormal Cst_L, only three had an abnormal $Cdyn_L$. We are not convinced that the patients described by Wilson et al. really had "normal mechanics of breathing", nor that D_{LCO} was the earliest abnormality detectable. The conclusion of Wilson et al. could not be confirmed by Ritchie (1964), who found that only two out of 22 patients with PSS had a reduced D_{LCO} as a single defect in pulmonary function.

We could not find any difference in pulmonary function between smokers and non-smokers, except for a slight, but significant, increase in V_D/V_T. The mild obstruction in our patients could not be explained by smoking. This finding contradicts that of Bjerke et al. (1979), who concluded that PSS generally does not lead to obstruction of peripheral airways, and that when obstruction is found, it can be attributed to concomitant cigarette smoking. Their smokers and non-smokers were, however, not comparable in such factors as lung volumes and elastic properties. These factors play an important role in the test they used to determine limited airway function. Variations in conductance of upstream segment are complex to interpret if elastic recoil differs in the different groups, as it did in the investigation of Bjerke et al. The interpretation of upstream resistance is still more difficult, if our assumption that the airways in PSS may resist compression is true.

We could not show any correlation between lung fibrosis and duration of the disease, again an example of varying progression of the disease, as has also been reported by others (Winkelmann 1976; Bagg & Hughes 1979).

In conclusion, we would emphasize that the most reliable test for defining the decreased lung function in PSS is to determine the static lung compliance. The fact that none of our patients reached 100 % of the predicted value indicated that pulmonary interstitial disease probably mostly fibrosis is a very common feature of PSS. Measurement of static lung compliance may be a test that comes close to expressing the amount collagen involvement. By combining the Cst_L with measurement of the VC, 13 patients proved to be abnormal. Very little extra information was obtained by more extensive examination. We did not find any patient with abnormal gas exchange due to PSS who did not have an abnormal Cst_L or VC. Since relatively little information is given by gas exchange studies, we advise restrictiveness with arterial punctures in these patients, who showed a marked tendency to long-standing vasospasm. In some patients, we found absence of A Ulnaris or a poor A Radialis. The risks for complication may be increased. In those patients where there may still be a need for studying the gas exchange, the best information is obtained by measuring the PaO_2 and $PaCO_2$ at rest and at maximal work. The sum (PaO_2 + $PaCO_2$) at rest indirectly reflects the $\Delta AaPO_2$.

ACKNOWLEDGEMENTS

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FACTORS LIMITING EXERCISE PERFORMANCE IN PROGRESSIVE SYSTEMIC SCLEROSIS

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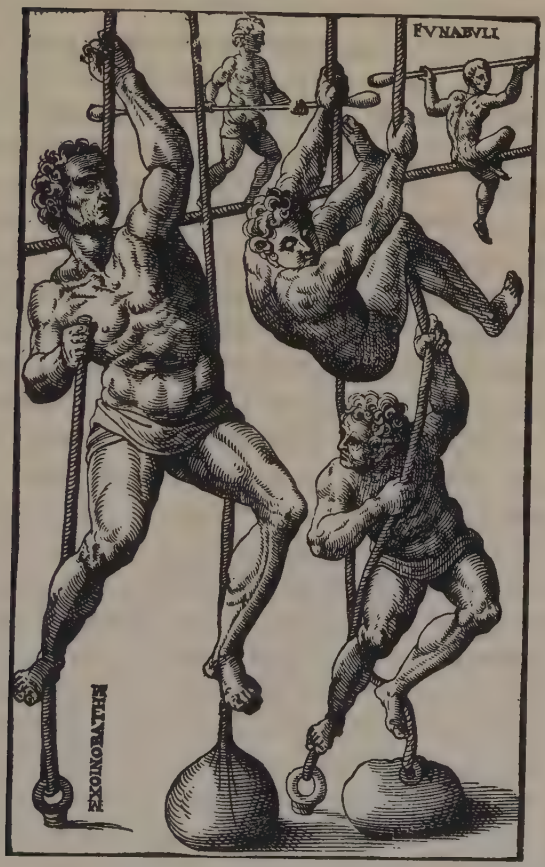

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ABSTRACT

In order to evaluate to which extent various organs limit physical performance in PSS, maximal working capacity was studied in 22 patients. Special attention was given to heart and lung function, joint mobility and muscular strength. A model for scoring these parameters is given. Working capacity was on the average 51 % of the predicted normal value. Ventilation at maximal work load was high despite normal arterial blood gases and presumably normal physiological dead space. This can be explained by an increased demand on ventilation from an increased muscle metabolism. This may be due to impeded mobility of respiratory and locomotive organs. The maximal heart rate was low and patients with low physical capacity had only a small fall in base excess. One third of the patients developed arrhythmia during exercise, which contributed to a low physical performance. Other myocardial involvement was common, seen in Q-waves, low voltage, left axis deviation and increased heart volume. In PSS, these ECG changes probably express myocardial fibrosis that has developed without clinically manifest infarction. Special attention must be paid to the arrhythmias, which are overlooked in a resting ECG. Ventricular tachycardia plays an important role in sudden death, which, when it occurs, almost always does so within the first years after the onset of PSS. There was no close linkage between heart dysfunction and lung fibrosis or joint-muscle impairment. The scoring system showed a rather equal distribution in reduction of working capacity as to circulation, to lung function and to locomotive function. Irrespective of the degree of work reduction, at least two organ systems were impaired in almost all of the patients. This emphasizes the complexicity of the disease already in its early stage.

Progressive systemic sclerosis (PSS, scleroderma) is a multiorgan disease. Fibrosis and changes in small vessels are prominent in various organ systems, such as the skin, heart and lungs (Rodnan 1963; Campbell & LeRoy 1975). Joint involvement often presents as a limitation of mobility caused by sclerosis of surrounding tissue or by secondary anchylosis. Skeletal muscles show fibrosis and degenerative changes in the muscle cells (Piper & Helwig 1955; Winkelmann 1976).

The disease often starts at an early age. It is, as a rule, slowly progressive over a long period of years. Limited physical capacity and other serious handicaps infer important social consequences. The patients are often unable to do any strenuous work.

The main goal of this study was to evaluate the extent to which the various organ manifestations contribute to this limitation of physical activity. We studied parameters describing the heart and lung function, joint mobility and the muscular strength in patients with PSS.

Well aware of the extreme difficulties to score such parameters, we have tried to grade the function deficits of various organ systems, and to determine their relative contribution to the limitation of physical activity.

PATIENTS AND METHODS

The patients fulfilled the criteria of PSS according to the American Rheumatism Association (Masi et al. 1980). All of the 22 patients had typical scleroderma and visceral involvement of at least one organ. Twenty patients had Raynaud's phenomenon. The eight men and fourteen women had a mean age of 49 years (range 23-69), and a mean duration of the disease of 6 years (range 1-17). The clinical features are presented in Table 1. There were eleven lifelong non-smokers, four smokers with an average tobacco consumption of 18 pack years and seven ex-smokers with an average of 13 pack years. The study was approved by the Ethical Committee of the University of Lund.

Table 1. Signs and symptoms in 22 patients with PSS.

	n	% of patients
Number of patients	22	
Males	8	36
Females	14	64
Raynaud's phenomenon	20	91
Skin tightness	22	100
Skin ulcerations	11	50
Joint stiffness	20	91
Weight loss $\geq$ 10 kg	7	32
Dysphagia	13	59
Antinuclar antibody	14	64

STATISTICAL METHODS

Student's t-test for paired and unpaired comparison, and single and double correlation tests were used (Snedecor 1956). Differences with a probability level $p < 0.05$ are marked with *, $p < 0.01$ with **, $p < 0.001$ with ***. $p > 0.05$ was considered not significant (N.S.).

SKIN AND JOINT FUNCTION

Skin involvement includes skin tightness and ulcerations. Joint mobility of the wrists was assessed by measurement of dorsal extension and volar flexion. Grip strength was recorded as the mean of three maximal compressions of a sphygmomanometer cuff inflated to 30 mm Hg (Lee et al. 1974).

LUNG AND HEART FUNCTION

Lung function tests included determination of total lung capacity, TLC, and residual volume, RV, in a whole body plethysmograph, while vital

capacity, VC, and forced expiratory volume in 1 s, FEV_1, were measured with a Bernstein spirometer. Elastic properties of the lungs were assessed from esophageal pressure related to lung volume. Static lung compliance, Cst_L, was calculated over the interval of 5-15 cm H_2O of the static pressure volume curve. Pulmonary resistance, R_L, was measured at rest and during graded exercise.

Arterial blood at rest and exercise was analyzed in a blood gas analyzer (Instrumentation Laboratory 613). These samples were taken from an ind-welling catheter in a brachial artery. Physiological dead space at rest was calculated from the composition of collected mixed expired gas (Scholander analysis) and from the average of five determinations of arterial gases during the collecting period.

The methods and the results from the lung function studies have already been described in greater detail (Blom-Bülow, Jonson & Brauer 1983, II).

Arterial arm blood pressure at rest was measured by auscultation. Chest radiography with determination of heart volume was performed.

EXERCISE TEST

The exercise test was performed in the sitting position on an electrically braked ergometer bicycle. ECG, heart rate and breathing frequency were recorded at rest and during work. Measurements were made of the flow rate at the mouth with a pneumotachograph and of esophageal pressure, Poe. Functional pulmonary resistance, Rf_L, dynamic pulmonary compliance, $Cdyn_L$, ventilation, $\dot{V}_E$, and dynamic flow volume curves were obtained after processing the signals in a computer connected on-line with the measurement equipment (Blom-Bülow, Jonson & Brauer 1983, II).

The starting load was, for most women, 30 W, and for men, 50 W. Some patients with low expected working capacity started at lower loads. After 4 minutes at each load, an arterial blood sample was drawn before measurement of the pulmonary mechanics. The patient worked about 5 min at each load. The load was then increased in steps equal to the starting

load until symtom limitation, or observations of severe heart arrhythmia, indicated interruption of exercise (two patients). If the patient was not able to work for 4 minutes, the value of the maximal working capacity was corrected in relation to the working time on the actual load.

ECG was continuously registered during work and up to 20 min after stopping. One investigator (BBB) recorded the subjective assessments of muscle fatigue and weakness, pain and general exhaustion, and dyspnoea. Subjective and objective reasons for stopping work were reported.

PREDICTED NORMAL VALUES

Most of our results are reported in % of predicted normal value in order to account for varieties of sex, age, height and weight, etc. This mode is expressed by the suffix %p, e.g. TLC %p.

Predicted values for various lung function tests were those used in the detailed study of lung function (Blom-Bülow, Jonson & Brauer 1983, II). Maximal heart rate at work (HR_{max}) was predicted after the formula given by Åstrand and Rodahl: HR_{max} = 210 - 0.76 x age (Åstrand & Rodahl 1970). Predicted maximal working capacity was determined according to Nordesjö (personal communication and Nordesjö & Landelius 1975), which implies that the younger, taller, heavier and more muscular a patient is, the greater the predictive working capacity will be. The upper limit for normal heart volume determined with chest roentgenogram was 500 ml for men, and 450 for women, per m^2 body surface area.

SCORING OF FACTORS LIMITING WORKING CAPACITY

The deficit in working capacity (ΔWC), in per cent of that predicted, corresponds to:

$$\Delta WC = 100 - \text{work performed \%p} \qquad \text{(Eq. 1)}$$

The important determinators of ΔWC; circulation, lung function and joint-muscle function were scored. The score for circulation is based upon the fall in base excess during exercise (ΔBE), maximal heart rate (HR_{max}, Fig. 1), arrhythmia at work and heart volume.

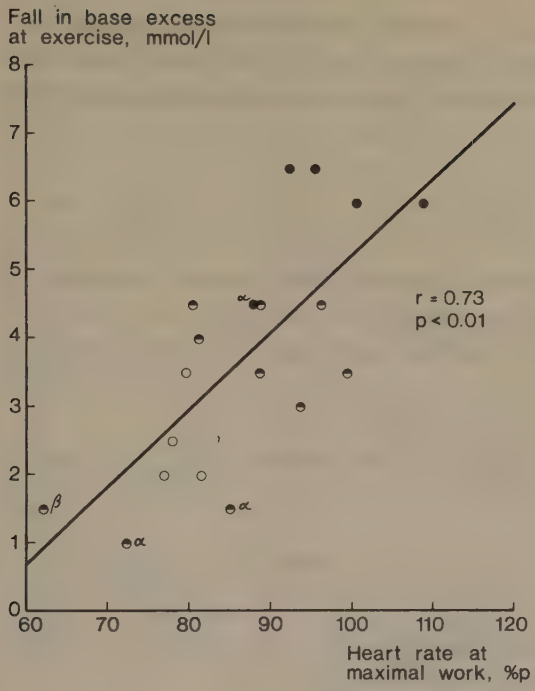

Fig. 1. The heart rate at maximal work %p, was correlated to the fall in base excess during exercise. The scoring of circulatory factors for exercise limitation was based mainly upon these results. A combination of a high heart rate and a pronounced fall of BE indicates that circulation was a limiting factor (score = 2, filled symbols). Low values indicate the opposite (score = 0, open symbols). Four patients with other indications of heart malfunction got higher scores than indicated by the heart rate and base excess. α indicates exercise arrhythmia of a degree that leads to interruption of exercise, and β a pronounced heart enlargement.

Scores of lung function were obtained mainly from the configuration of the dynamic P/V curves at maximal work (Figs. 2a and 2b) and from exercise hypoxia. Scores of joint and muscle function were based upon complaints of weakness, pain and general exhaustion during exercise.

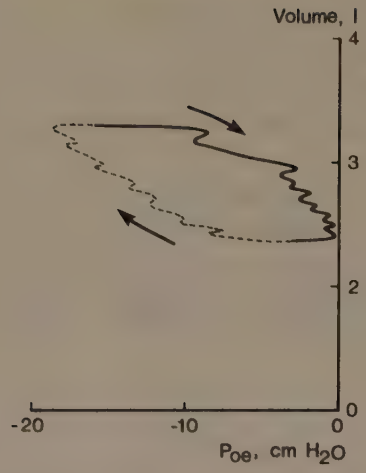

Fig. 2a.

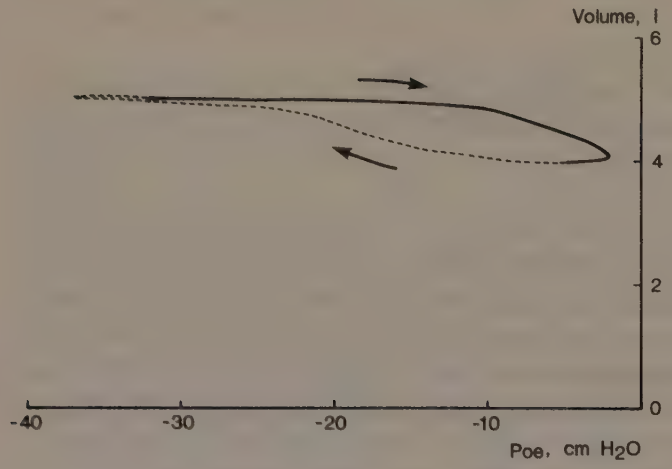

Fig. 2b.

Figs. 2a and 2b. The esophageal pressure, Poe, represents the transpulmonary pressure. Pressure-volume loops were obtained at the highest work load. Inspirations are shown in broken lines. Fig. 2a shows a pattern of moderate pressure changes associated with ordinary tidal volumes. This patient was not limited by pulmonary mechanics and got a score of "0" for lung function. The other patient, Fig. 2b, showed large pressure deviations with small tidal volumes. A low dynamic lung compliance was calculated. The score for lung function was "2".

Each of the three scored organ systems could yield 0 to 2 points of a total score. Zero means no contribution to work limitation. The deficit of working capacity referrable to each system was calculated from the equation:

$$\text{deficit}_{(\text{organ system})} = \Delta WC \times \frac{\text{score (organ system)}}{\text{total score}} \qquad \text{(Eq. 2)}$$

For example: A patient with a working capacity of 40 % of that predicted has a ΔWC of 60 %. If the score of the lung was 2, and the scores for circulation and joint-muscle function were 1 each, the deficit due to lung function was:

$$\text{deficit}_{(\text{lung})} = 60 \times \frac{2}{4} = 30 \text{ \% of predicted working capacity.}$$

RESULTS

All of the patients had a working capacity lower than that predicted. The mean was 51 % ($p < 0.001$, Table 2). The average maximal heart rate was lower than in healthy subjects ($p < 0.001$). The fall in base excess (ΔBE) was on the average 3.7 mmol/l, which is less than normal. There was a significant positive correlation between ΔBE and HR_{max} (Fig. 1), and between ΔBE and working capacity (Fig. 3). The breathing frequency (BF) at maximal work load was similar to that of normal exhausted subjects, but somewhat higher than normal in relation to the load. Ventilation at maximum load was 140 % of that predicted in relation to the load ($p < 0.001$).

In three patients with an advanced disease, we were unable to sample arterial blood, as a safe catheterization was not possible due to the status of the radial and ulnar arteries.

Mean values of PaO_2, $PaCO_2$ at rest were within normal limits (Table 3). PaO_2, however, did not rise during exercise, as it does in most normal subjects. Only one patient had a fall in PaO_2 that was large enough to

*Table 2. Individual values of maximal working capacity (load in watts), in per cent of that predicted (load %p), maximal heart rate (HR_{max}), in per cent of that predicted (HR_{max} %p), ventilation at maximal work ($\dot{V}_{Emax}$, ℓ/min), in per cent of that predicted ($\dot{V}_{Emax}$ %p), fall in base excess at maximal work (ΔBE) and breathing frequency at maximal work (BF_{max}). Significant differences from normal are indicated as: $p < 0.05$ *, $p < 0.01$ **, $p < 0{,}001$ ***. NS = not significant. Ci = circulation, Lu = lung function, Mu = joint-muscle function.*

Pat. n=22	Sex	Age	Load watt	Load %p	HR_{max}	HR_{max} %p	ΔBE mmol/l	BF_{max}	$\dot{V}_{Emax}$ ℓ/min	$\dot{V}_{Emax}$ %p	Scoring Ci	Lu	Mu
1	M	54	40	16	105	62	-1.5	47	50	281	1	1	1
3	F	44	120	76	170	96	-4.5	21	40	87	1	1	1
4	F	65	60	46	131	82	-2.0	28	37	160	1	0	1
5	F	54	90	72	150	89	-4.5	20	31	90	1	0	1
6	F	52	30	24	133	78	-2.5	25	29	177	0	1	2
7	M	69	60	41	134	85	-1.5	25	30	129	1	1	1
8	F	49	40	26	133	77	-2.0	24	35	197	0	2	1
9	F	42	90	68	158	89	-3.5	31	39	113	1	2	2
10	M	64	100	57	131	81	-4.0	28	52	135	1	2	1
11	F	39	60	33	169	94	-3.0	29	36	155	1	0	2
12	M	36	150	67	147	80	-4.5	27	57	100	1	1	1
13	F	46	60	49	154	88	-4.5	29	31	134	2	2	1
14	F	60	60	37	115	70	-	30	29	125	2	2	0
15	F	23	150	84	178	92	-6.5	34	52	91	2	1	1
16	M	40	150	67	143	80	-3.5	36	96	169	0	2	1
17	F	58	10	5	120	72	-1.0	29	28	207	1	1	2
18	F	37	60	30	120	66	-	23	22	95	2	2	0
19	M	56	120	61	160	96	-6.5	26	54	118	2	1	1
20	M	54	150	79	184	109	-6.0	29	55	97	2	1	0
21	F	56	90	64	138	82	-	27	38	110	0	2	0
22	F	45	60	36	175	100	-3.5	42	42	181	1	2	1
23	M	41	150	77	180	101	-6.0	30	78	137	2	2	1
$\bar{x}$		49.3	86	51***	147	85***	-3.7 N.S.	29	44	140***			
SD		11.1	44.1	22.6	22.9	11.8	1.73	6.3	17.5	47.7			

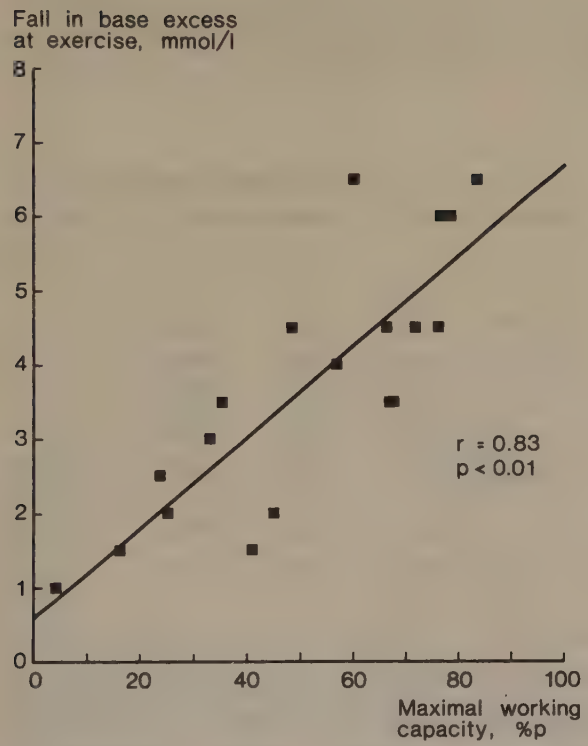

Fig. 3. Fall in base excess during exercise in relation to maximal working capacity.

signify desaturation of hemoglobine during work (PaO_2 at rest, 11.2 kPa; PaO_2 at work, 8.7 kPa). All of the patients had a normal hemoglobine concentration.

The reasons for stopping work are given in Table 4. The individual scores for each scored organ system are given in Table 2.

The static lung compliance was on average 66 % of that predicted ($p < 0.001$). All of the patients had lower Cst_L than predicted. Esophageal pressure at TLC was normal. Table 5 shows the data on lung function at rest.

*Table 3. Blood gases at rest and at maximal work. Significant differences of the mean from predicted values are indicated as: $p < 0,05$ *, $p < 0.01$ **.*

	PSS n=19		Predicted normal n=50	
	mean	SD	mean	SD
PaO_2 at rest, kPa	11.4	1.16	11.6	1.71
PaO_2 at max work, kPa	11.4**	1.08	12.3	1.10
$PaCO_2$ at rest, kPa	4.5	0.45	4.8	0.63
$PaCO_2$ at max work, kPa	4.4	0.57	4.7	0.60
$P_{A-a}O_2$ supine at rest, kPa	2.7**	1.07	2.1	0.95
V_D/V_T at rest	0.33	0.11	0.32	0.09

Table 4. Reasons for stopping work.

Exhaustion	Dyspnoea	Pain or weakness	Arrhythmia	Number of patients
x				6
x	x			7
x		x		3
	x			2
	x	x		2
	x		x	2
				22

Resting ECG showed pathological Q-waves in six patients, signifying infarction, and one patient had an abnormal R-wave progression in the chest leads (Table 6). Left axis deviation was the rule in these patients. Among the rest of the patients, the voltage of QRS complexes

was moderately low in two and markedly so in one patient. ST changes at rest were seen only in patients with signs of infarction. One patient had an AV block I. No other conductance defect was seen.

*Table 5. Pulmonary function data at rest. n = 22. Significant differences of the mean from predicted values are indicated as: $p < 0.05$ *, $p < 0.01$ **, $p < 0.001$ ****.*

	Mean	SD	Range
TLC %p	90**	15.2	61-115
RV %p	109	29.9	56-162
VC %p	87**	19.0	64-115
FEV_1 %p	93	19.3	63-126
Cst_L %p	66***	21.8	15- 96
R_L %p	180**	100	100-500

The fourteen patients with a normal resting ECG had an average heart volume of 74 % of upper normal limit, compared to 103 % in the others ($p < 0.001$).

The mean age of the patients with a normal ECG at rest was 44 years, compared to 58 years in the patients with pathological ECG ($p < 0.01$). The patients with a normal ECG had on the average a disease duration of 5.2 years, compared to 7.8 years in the others (N.S.).

No patient had arrhythmia at rest. At work, six patients developed marked arrhythmias with long periods of supraventricular (SVES) and ventricular (VES) extrasystoles in bigemini and/or trigemini or showers of extrasystoles of multifocal origin. After work, another patient got SVES with a mean frequency of two per minute, but no other pathological changes of the ECG. He is thus classified as a borderline case (Table 6).

Two patients, who developed extrasystoles in bigemini and/or trigemini during exercise, died suddenly of heart disease within two months after the test.

Table 6. ECG findings, history of myocardial infarction and heart volume in all of the patients. ++ indicates obvious and significant findings, + indicates borderline findings.

Pat. n=22	Infarction ECG	Infarction Clinical	Electrical axis frontal plane	Low voltage	Arrhythmia at work	Heart volume ml/m^2
1	++	++	-45^0	0	0	650
7	++	++	pos	++	++	450
4	++	0	-60^0	0	++	420
10	++	0	-75^0	0	0	530
14	++	0	0^0	0	++	500
17	++	0	-45^0	++	++	-
18	+	0	-15^0	0	++	510
13	0	0	pos	0	++	360
23	0	0	pos	0	+	390
21	0	0	pos	++	0	330
16	0	0	pos	+	0	410
22	0	0	pos	+	0	310
6	0	0	pos	0	0	320
3	0	0	pos	0	0	340
19	0	0	pos	0	0	-
5	0	0	pos	0	0	380
8	0	0	pos	0	0	300
9	0	0	pos	0	0	300
15	0	0	pos	0	0	320
11	0	0	pos	0	0	320
20	0	0	pos	0	0	320
12	0	0	pos	0	0	390

Two patients (Nos. 13 and 21) developed ST depressions and negative T-waves during or after work, as at coronary insufficiency, but did not report any chest pain.

Figure 4 shows that the scoring system about equally distributes the deficit of the working capacity between circulation, lung function and joint-muscle function. Two, or all three, of the organ systems contributed to the limitation of exercise in most of the patients.

Maximum working capacity showed a significant correlation to several parameters, such as maximum heart rate, fall in base excess, maximum ventilation, static lung compliance and vital capacity, grip strength and loss of weight (Table 7).

There was no correlation between maximal working capacity and duration of disease.

There was a positive correlation between joint movement and static lung compliance (r = 0.53*).

Table 7. Factors correlated to maximal working capacity in PSS.
HR_{max} %p = heart rate at maximal work in per cent of that predicted
V_{Emax} %p = ventilation at maximal work in per cent of that predicted
ΔBE = the difference in base excess at rest and at maximal work
r = correlation coefficient, y = a + bx, where x = maximal working capacity in per cent of that predicted

y	a	b	r	p
HR_{max} %p	67.7	0.34	0.65	< 0.01
ΔBE	-0.57	-0.06	0.83	< 0.01
$\dot{V}_{Emax}$ %p	219	-1.55	-0.74	< 0.01
Cst_L %p	39.56	0.52	0.54	< 0.05
VC %p	68.95	0.36	0.42	< 0.05
Grip strength	15.83	2.02	0.71	< 0.01
Weight loss	15.71	-0.18	-0.57	< 0.01

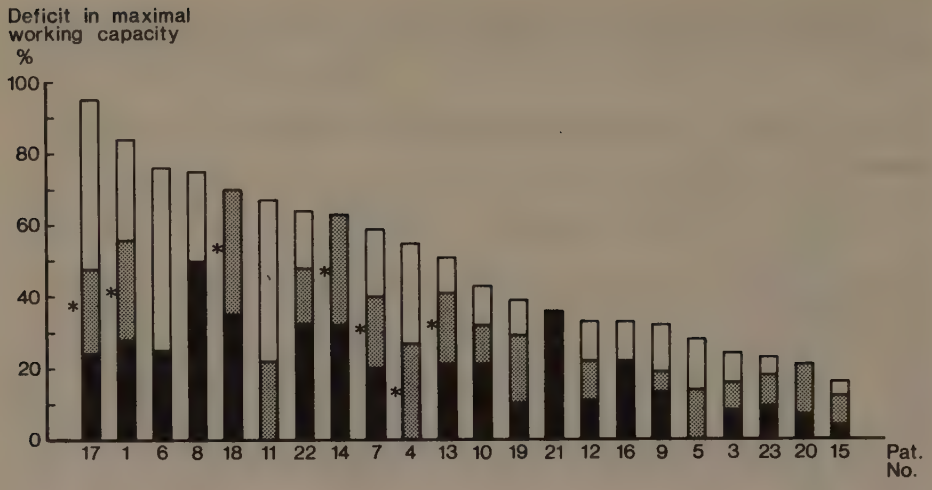

Fig. 4. The deficit in % of maximal working capacity referable to lung function (■), circulation (▩) and locomotive function (□). In patients marked with * , the circulation scores are mainly based upon arrhythmias at work. Arterial blood gases were not sampled in patients Nos. 14, 18 and 21.

DISCUSSION

The prediction of the normal working capacity of the patients was done according to the recommendations of Nordesjö, who utilized data from a number of studies comprising a vast number of subjects (Nordesjö & Landelius 1975). This system may lead to the risk for a too low prediction, since the patients with PSS have in general lost weight and muscle mass. In order to limit the influence of body mass, only classes II-IV of his original six classes of body build were used. Other systems for classification of working capacity have been tried. These efforts have confirmed that our prediction of working capacity is realistic. Our patients showed working capacities from nearly zero to values only slightly lower than those predicted.

The main feature of pulmonary dysfunction was in our patients found to be a low static lung compliance (Blom-Bülow, Jonson & Brauer 1983, II). All patients had a lower Cst_L than predicted, which may indicate that most of the patients or even all of them, had a pulmonary interstitial disease.

Our patients also had a slightly higher than normal pulmonary resistance (Blom-Bülow, Jonson & Brauer 1983, II). The changes of lung mechanics impede ventilation and increase the work of breathing. The importance of this impedance is enhanced by the fact that the patients with PSS have a much higher ventilation in relation to work load than normal subjects, as was also noted by Ritchie (1964) and Godfrey, Bluestone & Higgs (1969).

The fact that ventilation was 40 % higher than predicted during exercise is interesting. Total ventilation comprises dead space, $\dot{V}_D$, and alveolar ventilation, $\dot{V}_A$. The latter can be expressed as the quotient between the CO_2 elimination in liter/min, $\dot{V}_{CO_2}$, and the fraction of CO_2 in alveolar gas, F_ACO_2. Hence:

$$\dot{V}_E = \frac{\dot{V}_{CO_2}}{F_ACO_2} + \dot{V}_D \qquad \text{(Eq. 3)}$$

A normal physiological dead space at rest and normal arterial blood gases at exercise do not suggest any substantial increase above normal in dead space ventilation at work. Some increase of $\dot{V}_D$ may be due to the slightly higher breathing frequency than in healthy subjects. F_ACO_2 corresponds to $PaCO_2$ that in our patients was normal. The only remaining determinator of $\dot{V}_E$ is $\dot{V}CO_2$. A higher than normal $\dot{V}CO_2$ thus probably contributes to the increased demands on ventilation. $\dot{V}CO_2$ is an expression for aerobic metabolism. Impeded mobility of the respiratory and locomotive organs will lead to a high muscle metabolism in relation to the external work performed. In future studies of PSS measurements of oxygen uptake and CO_2 elimination test during exercise would be interesting.

Patients with the best working capacity had a fall of base excess similar to that of healthy subjects and a relatively high heart rate at maximal work. This indicates that these patients were close to their aerobic threshold, and that perfusion of their muscles was of importance for limitation of their working capacity, as it is in normal subjects. The patients with the lesser physical capacity had a small fall in base excess, but developed arrhythmia during exercise that leads to a low performance (Fig. 4).

It is known that PSS affects the heart and that it leads to myocardial fibrosis (Escudero & McDevitt 1958; Oram & Stokes 1961; Bulkley et al. 1976). D'Angelo et al. (1969) found myocardial fibrosis in 81 % of PSS patients, compared to 55 % in matched controls. Several reports (Bulkley et al. 1976; Barritt & O'Brien 1952; Fletcher & Morton 1967) point out proliferation of the connective tissue in the myocardium, which replaces the functioning muscular units. The low voltage seen in PSS patients has been associated with such morphological changes (Escudero & McDevitt 1958; Windesheim & Parkin 1958; Oram & Stokes 1961; Sackner, Heinz & Steinberg 1966).

It has also been reported that PSS patients have a tendency to shift the electrical axis to the left, like patients with arteriosclerotic heart disease (Sackner, Heinz & Steinberg 1966). In our study, only patients with ECG signs of myocardial infarction had a left axis deviation. Myocardial involvement shown by Q-waves, low voltage, left axis deviation, arrhythmia at work and increased heart volume were common.

More than one of these phenomena were usually present in each affected patient (Table 6). Infarction-like ECG changes in PSS may represent myocardial fibrosis that develops without clinically manifest infarction. More than 20 years after Oram's and Stokes' observation that ECG may indicate myocardial infarction in PSS patients without coronary symtoms (Oram & Stokes 1961), we do not know to what extent "infarctions" are secondary to vascular disease or not.

The patients with Q-waves or low voltage had not significantly different Cst_L from the other patients. Duska et al. (1982) did not find a correlation between vital capacity and the occurrence of defects in heart scans. His, and our, findings may imply that heart engagement is not closely linked with general fibroplasia.

We found arrhythmias at work in one-third of the patients. A high frequency of arrhythmias in PSS patients has been reported by Roberts et al. (1981) and Clements et al. (1981), who recorded a 24-hour ECG.

The difficulties to score each of the limiting factors only allow a restrictive interpretation of the data, and no detailed conclusions should be drawn. Figure 4, however, illustrates three main factors and functions which determine the physical capacity in the PSS patients. The nearly equal importance of the varying limiting factors underlines the complexity of the disease, and indicates the necessity of symptomatic treatment and physiotherapy to preserve the joint and muscle function, and to maintain the capacity of the respiratory and circulatory organs.

Special attention must be paid to the arrhythmias which are overlooked in a resting ECG. Sudden and unexpected deaths occur with some frequency in PSS (Bulkley, Klacsmann & Hutchins 1978; Marinato et al. 1981). It is notable that Clements et al. (1981) only found ventricular tachycardia within the first few years after the onset of PSS, which could imply that patients with this arrhythmia have shortened life spans. The two patients in our study who died showed ventricular tachycardia at work. They had been ill for three to four years. Treatment of the arrhythmias should be tried on the basis of proper diagnostic tests, i.e. exercise test with ECG and long-term ECG-recordings. As long as it can be assumed

that heart infarctions may develop on the basis of vascular malfunction, prophylactic treatment specific for this complication ought to be sought.

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EARLY CHANGES IN ESOPHAGEAL FUNCTION IN PROGRESSIVE SYSTEMIC SCLEROSIS

A COMPARISON OF MANOMETRY AND RADIOLOGY

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ABSTRACT

The characteristics of oesophageal dysfunction were studied with manometry and cine radiography in relation to clinical symptoms in 21 patients with typical progressive systemic sclerosis (PSS). Manometry was also performed in a matched control group. Only one patient had a completely normal manometry. Mean resting pressure in the upper and in the lower esophageal sphincters were significantly decreased in PSS. Twelve patients (58 %) had no detectable peristalsis in the lower esophagus. Special interest was focused on the upper esophagus, where the mean pressure amplitude of the peristaltic wave was found to be lower than normal in all patients with detectable peristalsis. The only feature of esophageal dysfunction observed in some patients was an increased speed of the peristaltic wave in the middle and lower esophagus. This is interpreted as an impaired coordination of the propulsive peristalsis. Neuromuscular dysfunction of the esophagus in its full length was clearly demonstrated in PSS. At cine radiography, three patients were judged as normal, and thirteen patients (62 %) had severe impairment of the peristaltic function in the distal two-thirds of esophagus. Hiatal hernia was found in six patients. An esophageal scoring based on manometry correlated well to scoring based on radiography. A proper radiographic technique including cine radiography of the recumbent patient gives adequate information for clinical purposes. To detect and quantify early changes in the amplitude and speed of the propagation wave, manometry is necessary.

Progressive systemic sclerosis (PSS, scleroderma) is a complex disease characterized by increased deposition of collagen, and vascular changes of varying degrees in several organ systems (Campbell & LeRoy 1975; Winkelmann 1976; Rodnan, Lipinski & Luksick 1979). The clinical features include Raynaud's phenomenon, skin tightness, joint stiffness and pain and dysfunction of visceral organs, particularly the esophagus, heart, lungs and kidneys (D'Angelo et al. 1969).

Esophageal involvement measured by manometry has been reported in up to 80 % of the patients with PSS (Saladin et al. 1966; Garrett et al. 1971; Turner et al. 1973). About 50 % of these patients had no esophageal symptoms. Impaired esophageal function is so typical for PSS that it is useful for the establishment of the diagnosis, although it has no effect on prognosis of survival (Garrett et al. 1971).

Complaints indicating esophageal involvement include solid food dysphagia, heart burn, feeling of fullness (early satiety) and occasional vomiting of undigested food shortly after meals.

One of the aims of the present study was to evaluate the characteristics of esophageal dysfunction more closely than in previous manometric studies. Another was to judge whether radiography and clinical evaluation of symptoms give information on esophageal function that is adequate for clinical purposes.

When esophageal function is studied by manometry, simultaneous intraluminal pressure recordings are performed at various levels to allow study of the amplitudes and the propulsive propagation speed of the peristaltic wave. In order to characterize early changes in esophageal function as closely as possible, an improved technique based on a central hole catheter device was used (Ulmsten 1974; Sundström & Ulmsten 1977). A control material of healthy subjects matched to our patients was also studied.

MATERIAL AND METHODS

Twenty-one patients with typical PSS according to the criteria of the American Rheumatism Association were included in the study (Masi et al. 1980). There were six men and fifteen women with a mean age of 46 years (range 23-72). The average duration of the disease was 6 years (range 1-17). Informed consent was obtained from all of the patients. The study was approved by the Ethical Committee of the University of Lund.

The clinical features of the PSS patients are presented in Table 1.

Esophageal manometry with identical technique was performed in twenty-one healthy volunteers, matched in regard to sex, age and smoking habits.

Table 1. Clinical features in the 21 patients with PSS.

	Number of patients	%
Raynaud's phenomenon	20	95
Skin tightness	21	100
Skin ulcers	10	48
Teleangiectasis	13	62
Weight loss $\geq$ 10 kg	7	33
Dysphagia	12	57
Heart burn	12 / 20	60
Early satiety	2	14
Vomiting	2	10

ASSESSMENTS

Radiography

The radiological evaluation was made by barium swallow examination while standing and in the supine position. The findings were recorded on full-size films and 35 mm cine fluorography. Propulsive peristalsis was studied with the patient in the prone position with the head lowered 10^{o}. The findings were classified by a four-grade scale where 0 was normal, and grade 1 indicated a sluggish, but clearly propulsive peristalsis throughout the esophagus. Grade 2 indicated some peristalsis in the upper part of the esophagus, but mostly segmental contractions with no obvious propulsive effect in the lower part. Grade 3 implied that peristalsis had ceased. In addition, the presence of strictures and hiatal hernia with or without reflux were registered. A routine chest radiograph was included. Judgement of the esophageal radiography including cine radiography was done on one occasion by the same trained physician. The original interpretation of fluoroscopy was used in three patients, since the cine films were not available.

Esophageal manometry

Esophageal motility, including the activity in the upper and the lower esophageal sphincters (UES and LES, respectively), was studied with a central hole catheter device and the pressure-recording technique described earlier (Sundström & Ulmsten 1977). Manometry was performed with the patient resting in the supine position. The transducers were adjusted to the mid-thoracic level. The three recording apertures were initially positioned in the stomach. The following procedures were then carried out twice:

1. The middle opening of the catheter was positioned in the high pressure zone of LES near the pressure inversion point between the abdomen and the thorax. The resting activity was recorded for one minute.

2. The catheter was then positioned at three levels, with the middle aperture 4, 8 and 12 cm above LES referred to as lower middle and upper esophagus. The peristaltic wave was recorded twice at each level (9-4, 13-8, 17-12 cm above LES) after swallowing 5 ml water of room temperature.

3. The middle opening of the catheter was positioned in the UES, i.e. at the level of the maximum resting pressure just below the pharynx. The resting activity and the amplitude of the swallowing of the 5 ml of water were then registered.

The resting pressure in LES was defined as the mean of the two registrations of the resting pressure averaged through the respiratory cycle. The average gastric fundal pressure was used as the zero reference. The resting pressure in UES was measured relative to the esophageal pressure 5 cm below the sphincter. The peristaltic amplitude was measured from the peak of the pressure wave relative to the resting esophageal pressure at the same level.

Peristaltic propagation speed was calculated from the time taken for the pressure peak to travel from the upper to the middle apertures of the catheter (Fig. 1).

The results of esophageal manometry were scored for each patient. Normal function was scored as zero. As will be discussed, a higher than normal propagation speed indicates a dyscoordination of esophageal activity. A propagation speed of the pressure wave exceeding the normal range (95 % confidence interval) contributed to the score by 1 point. An amplitude below the normal range added 2 points to the score. High speed combined with low amplitude or the absence of contractions observed at one or two levels gave 3 points. No recorded activity rendered 4 points (Fig. 2).

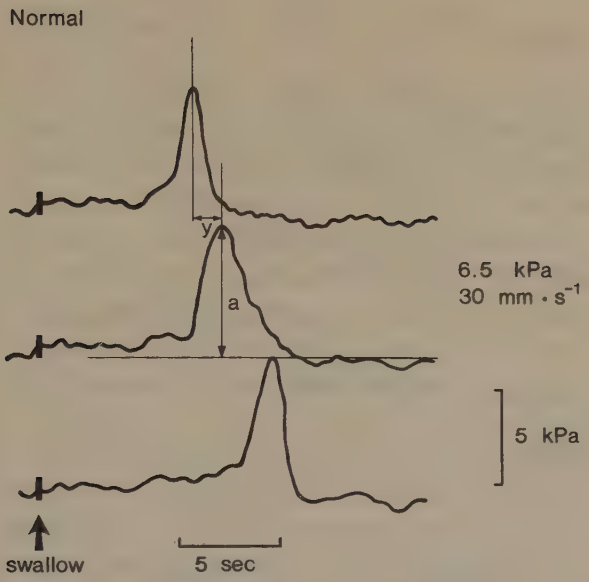

Fig. 1. A normal peristaltic wave in the esophagus. The upper tracing refers to the recording from the most proximal catheter hole. Following a swallow, separation of the three wave peaks in time is clearly seen. The propagation speed is calculated as x/y, where x is the distance in mm between the catheter holes. y is the time in seconds between the wave peaks. a = the amplitude of the pressure wave.

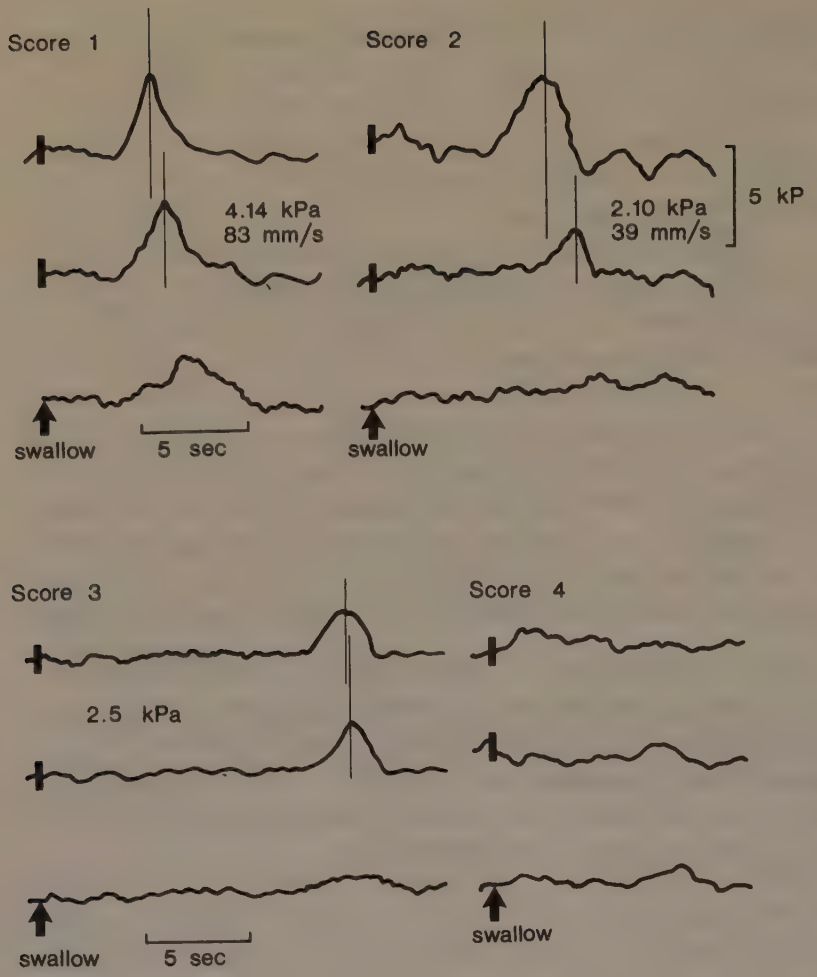

Fig. 2. Different patterns of the peristaltic wave in the esophagus, on which the manometry scoring was based. The upper tracing refers to the recording from the most proximal catheter hole.

Upper left: A high propagation speed exceeding the normal range gave a score of 1.

Upper right: An amplitude below normal range added 2 points to the score.

Lower left: High speed (approaching infinity) and low amplitude rendered 3 points.

Lower right: No detectable propagation wave gave a score of 4.

Clinical scoring of esophageal involvement

Scoring of clinical symptoms and signs of disease is difficult. We have made a clinical scoring system based foremost on the symptoms and signs directly referred to the esophagus, such as dysphagia, heart burn, early satiety, and vomiting. On the other hand, indirect parameters, such as weight loss and the duration of the disease were also taken into account. We found it relevant to include the duration of the disease in a clinical scoring system as esophageal impairment has been said to be invariably progressive with time in PSS, even in cases where the skin involvement has improved (Garrett et al. 1971).

Dysphagia was assigned major importance in the total score, and was arbitrarily given 5 points. The other subjective symptoms gave 1 point each. Weight loss could be scored up to 4 points (1 point per 5 kg weight loss), and the duration of disease maximally 3 points (duration less than 6 years = 1 point; 6-10 years = 2 points; more than 10 years = 3 points).

Lung mechanics and physical working capacity

Lung function was analysed in a separate study (Blom-Bülow, Jonson & Brauer 1983a). Total lung capacity, residual volume and functional residual capacity were measured in a whole-body plethysmograph. Static lung compliance was calculated for the interval of 5-15 cm H_2O in a static recording of lung volume versus pulmonary static recoil pressure.

The patients also performed an exercise test on a bicycle ergometer. Factors limiting the physical working capacity have been studied in detail (Blom-Bülow, Jonson & Brauer 1983b).

Statistical methods

Student's t-test for paired and unpaired comparison, single correlation, Spearman's correlation and Mann Whitney's U-test were used (Snedecor 1956; Siegel 1956). Differences with a probability level of $p > 0.05$ were considered non-significant (NS).

RESULTS

Radiology

Table 2 shows the individual results of the radiological examination. A hiatal hernia was found in six patients. Two of these six had also gastric esophageal reflux, and one had an esophageal stricture.

Three patients had a normal radiography. Air in the esophagus, which is regarded as a particular feature of PSS (Dinsmore, Goodman & Dreyfuss 1966; Henderson 1976), was observed in two patients one of whom had a normal cine fluorography. Thirteen of the patients had severe impairment of the peristaltic function, and got 2 or 3 points in the radiological scoring.

Table 2. Radiological findings, manometric and clinical scores of esophageal involvement in the PSS patients. G-E indicates gastro esophageal reflux.

Patient number	Hiatal hernia	G-E reflux	Radiography score	Manometry score	Clinical score	Dysphagia
3	0	0	1*	2	2	-
4	0	0	2	4	3	-
5	1	**	2	4	9	+
6	1	1	3	4	8	+
7	1	0	1	4	3	-
8	0	0	1	1	9	+
9	0	0	0	1	4	-
10	1	0	2	1	2	-
11	0	0	3	4	8	+
12	0	0	2	4	12	+
13	0	0	3	4	10	+
14	0	0	3*	4	4	-
15	0	0	0	1	1	-
16	0	0	1	2	7	+
17	0	0	3	4	13	+
18	0	0	1	3	9	+
20	0	0	2	0	1	-
21	1	1	2	3	11	+
22	0	0	3	4	11	+
23	0	0	0	1	8	+
24	1	0	2	3	4	-

* Air in the esophagus on a lateral chest radiogram
** Stricture in the distal esophagus made judgement of GE reflux impossible

Manometry

Table 3 shows the results of the controls. Neither age nor sex correlated to the manometric results.

Table 3. Results in 21 normal subjects. Esophageal sphincter pressures were measured at rest. Amplitudes and propagation rates of the peristaltic wave after swallowing.

	Mean	SD	Observed range
Upper sphincter (kPa)	2.7	0.95	1.3 - 5.1
Lower sphincter (kPa)	0.93	0.45	0.34 - 1.8
Peristaltic pressure amplitude (kPa) at			
upper esophagus	6.2	1.6	4.4 - 10.0
middle esophagus	6.2	1.8	3.0 - 9.6
lower esophagus	5.7	1.8	2.2 - 8.1
Propagation rate (mm x s^{-1}) at			
upper esophagus	31	7.9	19 - 46
middle esophagus	32	7.9	20 - 50
lower esophagus	28	6.6	16 - 37

The resting pressure in the PSS patients in the upper sphincter was 1.4 ± 0.55 kPa, and was significantly lower than that of the controls ($p < 0.001$). The resting pressure in the lower esophagus sphincter was also subnormal, 0.37 ± 0.31 kPa ($p < 0.001$). The wide spread of the values observed in both controls and in PSS patients reduces the value of the information on resting sphincter pressures in a single patient.

Only one patient had a completely normal peristaltic function (score 0). Ten patients had a reduced function (score 1-3) and ten other patients had no detectable peristalsis (score 4) (Fig. 2).

Fig. 3 shows that the amplitude of the peristaltic pressure wave was significantly lower than normal in the upper and middle esophagus ($p < 0.05$ Mann Whitney U-test).

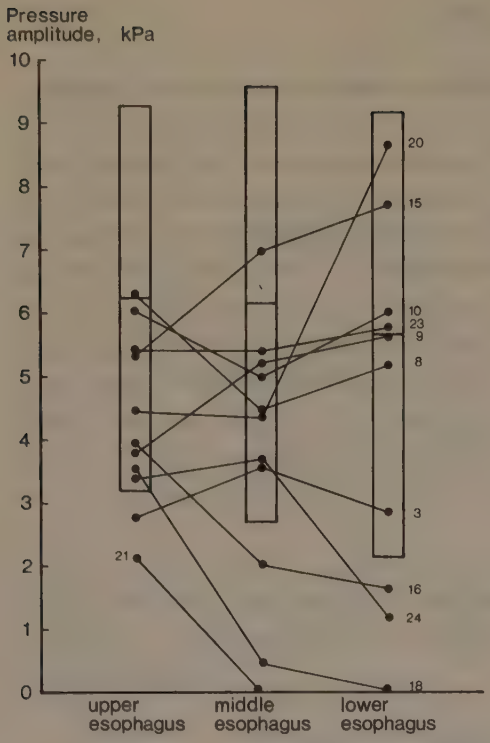

Fig. 3. The peristaltic pressure amplitude recorded at three levels of the esophagus. The normal range (95 % confidence interval) is indicated, as are individual values for the PSS patients. Ten patients with aperistalsis were excluded.

Only seven patients had an amplitude within normal limits in the lower esophagus. Five of these patients had an abnormally high speed at that level (Fig. 4). The speed of the peristaltic wave was significantly higher than normal at the middle and lower levels of esophagus among patients with a detectable esophageal contraction ($p < 0.05$ Mann Whitney U test).

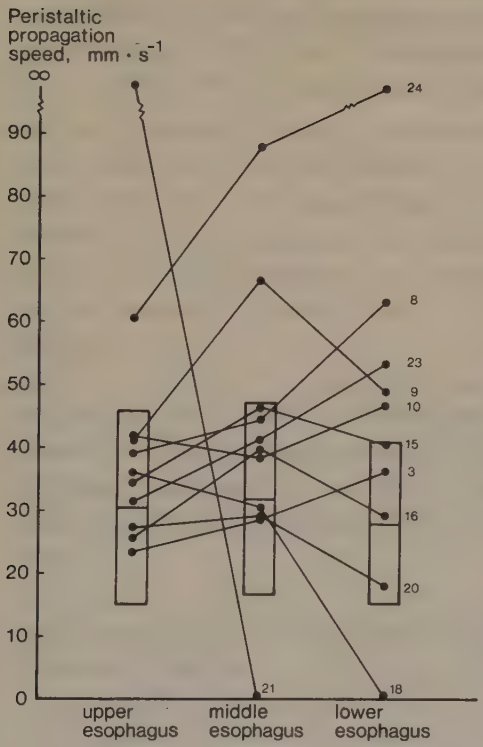

Fig. 4. The peristaltic propagation rate at three levels of the esophagus in the eleven patients with detectable pressure waves. The normal range (95 % confidence interval) is indicated, as are individual values for the patients. The two indications of "infinite speed" refer to curves with simultaneous contractions at the two points where the propagation speed was measured.

Clinical score and correlation to manometry and radiology

Twelve patients complained of dysphagia (Table 2). This symptom together with other esophageal symptoms contributed with 77 points to the clinical score. Weight loss added 30 points and duration of disease 33 points; in total 139 points.

Both the clinical score for esophageal involvement and the radiographic score correlated fairly well with the manometric score (Fig. 5). Such correlations were not found if manometric amplitudes and propagation rates were evaluated separately.

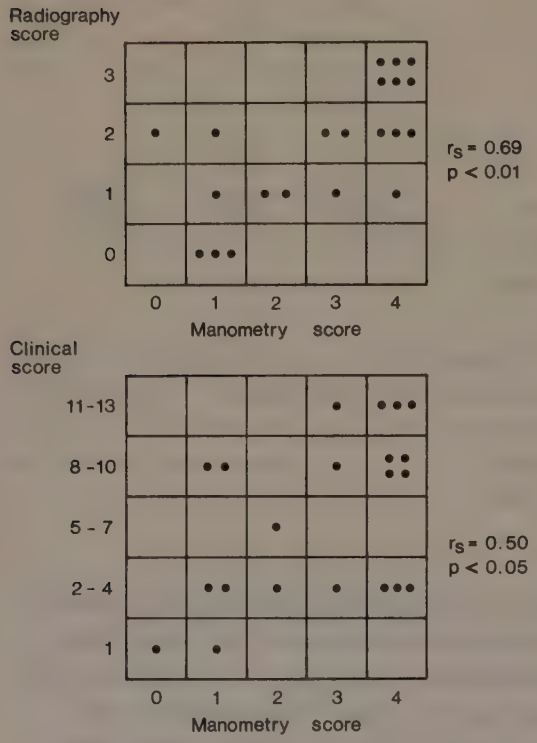

Fig. 5. Correlation between manometry score and radiographic and clinical score in the PSS patients. r_s is the Spearman correlation coefficient.

This study was part of a comprehensive investigation of the physiological characteristics of PSS patients. Data from that study were compared with the esophageal function (manometry score).

Both the working capacity and the grip strength of the hand (Blom-Bülow et al. 1983b) correlated fairly well with the manometry score ($p < 0.05$). Eight patients had pathological Q-waves and/or low amplitude of the QRS-complexes in their ECG as a sign of myocardial damage. Seven of them had a manometry score of 3 or 4.

The main feature of pulmonary dysfunction in our patients was a low static lung compliance. It was on the average 64 % of the predicted normal value (Blom-Bülow, Jonson & Brauer 1983a). Static lung compliance showed a range from 15-89 % of the predicted normal value among the patients with aperistalsis. There was absolutely no correlation between static lung compliance and the manometric findings. Nor was clinical score related to static lung compliance.

The patients were thoroughly investigated for signs of malnutrition (Blom-Bülow et al. 1981). No significant correlations were obtained between esophageal involvement and different biochemical parameters, such as serum hemoglobine, cobolamine, folic acid, gastrine or fecal free fatty acids.

The kidney function studied with Cr-EDTA clearance did not correlate to esophageal function.

DISCUSSION

Investigation of esophageal function by manometry is an accepted procedure for evaluating various esophageal disorders, but involves problems of standardization and technique (Bombeck, Battle & Nyhus 1973; Kaye 1973; Turner et al. 1973; Zabinski, Spiro & Biancani 1975). When comparing data, it is necessary to know the exact technical details. A conventional catheter with lateral holes in the distal ends is frequently used in esophageal manometry. The outward position of the recording holes can, however, lead to mucosal interference. We used a catheter with the orifices directed toward the centre of the catheter bundel, which was thus protected from the mucosa. With a centre-hole catheter, the resting pressures of the esophageal sphincters are generally lower, but the peristaltic amplitudes are similar in the two catheter systems (Sundström & Ulmsten 1977).

At post mortem examination, atrophy is the predominant smooth muscle abnormality found in the esophagus. The esophagus wall is not fibrotic and rigid, but flaccid, due to destroyed muscles (Treacy et al., 1963; D'Angelo et al. 1969). Deposition of collagen is not a prominent feature (Henderson 1976).

Turner et al. (1973) state that the development of esophageal dysfunction in PSS starts with a subnormal resting pressure of the lower esophageal sphincter and lower peristaltic pressure amplitudes in the distal esophagus. Absent distal esophageal peristalsis, together with reduced resting pressure in the lower esophagus sphincter, is claimed to be pathognomonic for PSS (Turner et al. 1973). The present study supports many of Turner's conclusions, but also gives facts for describing esophageal involvement in more detail.

Little attention has previously been given the upper part of the esophagus, which is mostly composed of striated muscle. Garrett et al. (1971) and Hurwitz, Duranceau & Postlethwait (1976) did not find any dysfunction. Atkinson and Summerling (1966) reported a failure of contractions in the upper esophagus in five patients, in whom the striated muscle was histologically normal.

In our study, the pressure amplitude of the peristaltic wave in the upper esophagus was clearly lower in the group of 11 patients with peristalsis than in the normal subjects (Fig. 3). If we regard single patients, most of them did not have an amplitude of the pressure wave below the normal range in the upper esophagus. Engagement of the upper esophagus in PSS was established in this study by direct comparison with the matched controls. In individual patients with peristalsis, esophageal dysfunction was, however, more easily observed in the lower esophagus. Some (Nos. 3, 16, 18, 21, 24 in Fig. 3) had a poor pressure amplitude that faded out in the lower parts, as has previously been described by several authors (Saladin et al. 1966; Neschis et al. 1970; Garrett et al. 1971; Turner et al. 1973; Hurwitz et al. 1976; Cohen 1979). The other six patients (Nos. 8, 9, 10, 15, 20 and 23) had normal or even high amplitudes. Five of these patients had a propagation speed in the lower esophagus at the upper normal limit or even higher. An increased speed of the peristaltic wave in the middle and lower esophagus was the only abnormal parameter in some patients. The increased speed is, of course, not a sign of increased function, but must rather be interpreted as an expression of an impaired coordination of the propulsive peristalsis. In the two cases with "infinite speed", all propulsion must reasonably be absent.

Histological studies (Atkinson & Summerling 1966) and the present data support the concept that the function of the esophagus in its full length is disturbed in PSS, and that the cause of the dysfunction lies in the neuromuscular mechanisms. These mechanisms depend upon innervation, myogenic activities and circulation of humoral substances (Cohen 1979). A weak initial stimulation of muscular activity in the upper esophagus may give a poor contraction in the lower esophagus (Sarna, Daniel & Waterfall 1977). The particularly poor function of lower esophagus in our patients can thus partly reflect a poor initialization of a peristaltic wave in the upper esophagus. In later stages of PSS, the absence of esophageal peristalsis may be associated by muscular atrophy.

Significant correlations existed between esophageal involvement and striated muscle function parameters, such as grip strength and maximal working capacity. ECG signs of myocardial involvement were furthermore common in patients with prominent esophageal dysfunction. There appears

to be a link between the dysfunction of striated muscles in different organs in PSS.

We did not find any correlation whatsoever between lung fibrosis and esophageal dysfunction. This contradicts the hypothesis of Denis et al. (1981), who claimed that lung fibrosis in PSS is the result of chronic aspiration of the gastric contents. We found no correlation, either, between esophageal involvement and joint mobility, another parameter indicating fibrotic changes. All of these findings suggest that esophageal dysfunction is closer linked to neuromuscular function than to the fibrotic features of the disease.

The loss of motor power in the esophagus, demonstrated either by manometry or by radiography, does not always produce symptoms, as has also been reported by others (Stevens et al. 1964; Saladin et al. 1966, Garrett et al. 1971; Krejs et al. 1976). On the whole, esophageal manometry showed a correlation to our clinical esophageal scores (Fig. 5).

The most characteristic radiologic finding in PSS is the loss of effective peristalsis in the distal part of the esophagus, accompanied by dilatation and delayed emptying. When using heavy barium contrast medium, these observations may be missed in the erect position. The patients should thus always be examined in recumbent or prone positions, with the head slightly lowered. Radiology also detects the presence of hiatus hernia, reflux, and stricture and may give information on associated malignancy. Frequencies of hiatal hernia in PSS have been reported from 30 to 50 % (Fraser 1966; Garrett et al. 1971). In this study, six patients (29 %) had a hiatal hernia. It must be stressed that the reported prevalence of hiatal hernia is closely related to the method used. With a technique similar to ours, Mandelstam and Lieber (1970) reported hernia in 52 % of male and 26 % of female normals, using cine fluorography. With a manometry technique, Kjellén and Tibbling found only 14 % hiatal hernia in a middle-aged general population in spite of abdominal compression that would increase the incidence (Kjellén & Tibbling 1981). Available data do not allow the conclusion that the incidence of hiatal hernia is increased in PSS.

A close correlation between the results of cine radiography and of esophageal manometry was obtained in the present study. Earlier studies

with conventional barium esophageal radiography have proven to be of limited value in comparison with manometry for detecting esophageal disease (Neschis et al. 1970). Our results show, however, that a proper radiographic technique including cine radiography gives adequate information on esophageal function for clinical purposes.

Esophageal manometry is suitable for research purposes for detecting e.g. an increased propagation speed or for quantitating changes in esophageal involvement after treatment. It could also be used as a diagnostic tool, especially in cases of PSS without typical skin changes (Turner et al. 1973).

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